The SSTARS (STeroids and stents Against Re-Stenosis) Trial: Different stent alloys and the use of peri-procedural oral corticosteroids to prevent in-segment restenosis.

ADAM, ZULFIQUAR

The SSTARS (STeroids and stents Against Re-Stenosis) Trial: Different stent alloys and the use of peri-procedural oral corticosteroids to prevent in-segment restenosis.

A thesis submitted for the degree of Doctor of Medicine

2016

Durham University

by

Dr. Zulfiquar Adam MBChB, MRCP

Cardiothoracic Division

The James Cook University Hospital

Middlesbrough

United Kingdom

Supervisors

Professor A.P.S. Hungin OBE DL MD FRCGP FRCP FRSA

School of Medicine, Pharmacy and Health

Durham University

Wolfson Building, Queen's Campus

Stockton on Tees

Dr. M.A. de Belder MA MD FRCP

Consultant Cardiologist

The James Cook University Hospital

Middlesbrough

Declaration

The research contained in this thesis was carried out by the author whilst a postgraduate student in the School of Medicine and Health at Durham University. None of the work has been submitted in candidature for any other degree.

Statement of copyright

Acknowledgement

This thesis would not have been possible without the guidance, enthusiasm and critical appraisal provided by my supervisors Dr M. A. de Belder and Professor A.P.S. Hungin. I benefitted greatly from their vast experience in clinical research and they were always available to steer me in the right direction. Dr de Belder has also supported me greatly throughout my many years of training and research at The James Cook University Hospital and has been an integral part in my development.

I would also like to thank Dr. Andrew Turley who suggested the topic and all of the interventional cardiologists at The James Cook University Hospital and the Royal Infirmary of Edinburgh for their support in recruiting patients for the study.

I am also beholden to Professor James Mason and Dr Adetayo Kasim of the clinical trials unit at Durham University who provided invaluable statistical support.

I am also grateful to Mrs. Laura Thompson and Mr. Robert Morley as well as Sister Bev Atkinson, Mrs. Sue Metcalfe and the research nurse team in the Cardiothoracic Division of The James Cook University Hospital who assisted greatly in data collection, data entry and management of the trial.

I am also indebted to my parents for their encouragement and financial support and appreciate the support from my brothers, Asif and Safwaan.

Finally, I would like to thank my wife, Asma, for all her support and understanding throughout the process.

Contents

Abbreviations

ACC/AHA	American Heart Association/American College of Cardiology
ACS	acute coronary syndrome
BMS	bare metal stent
CABG	coronary artery bypass grafting
CRP	C Reactive Protein
C-SES	Cypher sirolimus eluting stent
DAPT	dual antiplatelet therapy
DES	drug eluting stent
ECM	extracellular matrix
E-ZES	Endeavor zotarolimus eluting stent
ESC	European Society of Cardiology
GR	glucocorticoid receptor
hs-CRP	highly sensitive CRP
HPA	hypothalamic pituitary adrenal
ISR	in-stent restenosis
IVUS	intravascular ultrasound
MACE	major adverse cardiovascular events

MACCE	major adverse cardiovascular and cerebrovascular events
MI	myocardial infarction
MLD	minimal luminal diameter
MR	mineralocorticoid receptor
NAD	nicotinamide adenine dinucleotide
NADPH	nicotinamide adenine dinucleotide phosphate
NICE	National Institute of Health and Care Excellence
PCI	percutaneous coronary intervention
PTCA	Percutaneous transluminal coronary angioplasty
QCA	Quantitative coronary angiography
R-ZES	Resolute zotarolimus eluting stent
SMC	smooth muscle cell
TLR	target lesion revascularisation
T-PES	Taxus paclitaxel eluting stent
TVF	target vessel failure
TVR	target vessel revascularisation
X-EES	Xience V everolimus eluting stent
11β-HSD	11β-hydroxysteroid dehydrogenase

INTRODUCTION

I am a specialty training registrar in the Northern Deanery training in interventional cardiology. There is a strong emphasis on research within the cardiology unit at The James Cook University Hospital and when I joined, initially as a clinical registrar, I was presented with an opportunity to undertake clinical research. This led to my interest in this project. The SSTARS (STeroids and stents Against Re-Stenosis) Trial was at an early stage when I joined the unit in my role as research fellow. The trial structure and committees are described in section 2.2. As one of the investigators I was involved with the design of the trial, trial protocol, recruitment, data collection, analysis and interpretation.

Abstract

Stent design and technological modifications to allow for anti-proliferative drug elution influence restenosis rates following percutaneous coronary intervention (PCI).

The main aim of this study was to investigate whether peri-procedural administration of corticosteroids or the use of thinner strut cobalt alloy stents would reduce rates of binary angiographic restenosis (BAR) after PCI. In addition, the role of the acute phase highly sensitive C-Reactive protein (hs-CRP) in restenosis in bare metal stents (BMS) was also investigated. This was a two centre, mixed single and double blinded, randomised controlled trial using a factorial design.

The use of prednisolone was compared against placebo, starting at least six hours pre-PCI and continued for 28 days post-PCI. Additionally, cobalt chromium (CoCr) stents were compared to stainless steel (SS) alloy stents, in patients admitted for PCI. The primary end-point was BAR at six months.

Three hundred and fifteen (359 lesions) were randomly assigned to either placebo (n=145) or prednisolone (n=170) and SS (n=160) or CoCr (n=160). The majority (58%) presented with an acute coronary syndrome (ACS), 11% had diabetes and 287 (91%) completed angiographic follow up. The primary endpoint, binary angiographic restenosis, occurred in 26 cases in the placebo group (19.7%) versus 31 cases in the prednisolone group (20.0%) respectively, p=1.00. For the comparison between SS and CoCr stents, BAR occurred in 32 patients (21.6%) versus 25 patients (18.0%) respectively, p=0.46.

Hs-CRP was monitored at 5 points during the trial. The pre-PCI hs-CRP measurement was ≤5mg/l in 213 patients (71%) of whom only 28 (13%) had a raised CRP at day 7. There was some evidence of prednisolone suppressing hs-CRP response at day 7 (-5.98 mg/L, 95%CI: -8.35 to -3.61, p<0.001). There was no correlation between lowering hs-CRP and stenosis diameter at follow-up.

This study showed that treating patients with a moderately high dose of prednisolone to cover most of the period of inflammation associated with restenosis in BMS did not reduce the incidence of BAR. There was also no significant reduction in six month BMS restenosis rates with stents composed of CoCr alloy compared to SS alloy and no observed relationship to hs-CRP.

Research Questions

a) To investigate whether the peri-procedural use of oral corticosteroids in elective/acute patients undergoing percutaneous coronary intervention would reduce the incidence of in-segment re-stenosis.

b) To investigate whether the use of cobalt chromium stents results in lower restenosis rates than stainless steel stents in elective/acute patients undergoing percutaneous coronary intervention.

c) To investigate whether elevated systemic levels of highly sensitive C-Reactive Protein resulting from coronary plaque disruption will be associated with degree of restenosis at follow-up and whether there is any relationship to oral steroid therapy.

Aims

Primary aims

The primary aims of the SSTARS study were twofold. The first was to evaluate the use of peri-procedural corticosteroid administration versus placebo on the incidence of coronary artery in-segment restenosis rates following PCI. The second was to compare the incidence of coronary artery in-segment restenosis rates between chromium cobalt and stainless steel bare metal stents.

Secondary aims

The secondary aims were to evaluate the use of peri-procedural corticosteroid administration versus placebo and to compare chromium cobalt and stainless steel bare metal stents with regards to the following endpoints:

- Late loss, defined as the difference between minimum lumen diameters after the index PCI and at follow up.
- Target lesion revascularisation, defined as repeat intervention of restenotic lesions, which include the target site of the stent implantation or 5mm proximal and distal in the same epicardial coronary artery.
- Target vessel revascularisation, defined as repeat intervention within the same epicardial coronary artery.
- Incidence of death.
- Myocardial infarction (MI*) – classified as fatal or non-fatal and whether related to the target vessel or not
- Unstable angina.
- Cerebrovascular accident (CVA).
- Repeat hospitalisation.
- Major/minor bleeding complications.
- Poor glycaemic control.

*A new MI was defined by the presence of at least two of onset of typical ischaemic chest pain lasting > 20 minutes, typical ECG changes i.e. ST elevation/ new LBBB and elevation in cardiac markers (Troponin T > 0.1ng/ml)

CHAPTER 1

Review of literature

1.1 The evolution of percutaneous coronary intervention relative to restenosis

Percutaneous transluminal coronary angioplasty (PTCA) was first performed in the late 1970s by Dr. Andreas Gruentzig and colleagues (1). They were able to successfully dilate initially focal atherosclerotic segments of coronary arteries using specially modified catheters and balloons in the majority of patients undergoing the procedure. However, abrupt arterial closure resulting from coronary dissection, coronary vasospasm and thrombus formation were limitations of PTCA (2, 3). Consequences included acute myocardial infarction and emergency coronary artery bypass grafting (CABG) (4, 5). A later complication of PTCA was the gradual recurrence of stenosis appropriately referred to as restenosis. In Gruentzig's original series of patients, 31% of patients who had follow up coronary angiograms at 6 months had restenosis (6). Another group also noted a similar rate of restenosis (7).

An understanding of the underlying mechanism of restenosis was necessary to improve the success of PTCA. One factor thought to be implicated was elastic recoil of the dilated vessel following balloon inflation. This began early, within days of the procedure (8). A second mechanism was the development of what would later be termed neointimal formation (see section 1.3). The prevailing theory was that an inflammatory cascade initiated by injury to the arterial vessel wall as a result of PTCA resulted in the formation of a new fibro-proliferative layer leading to a reduction in the lumen of the vessel (9, 10). A third mechanism was negative arterial remodelling after PTCA, "vessel shrinkage", which was measured with intravascular ultrasound (11).

Following an understanding of the causes of restenosis, other modalities of vessel dilation were explored, including atherectomy, laser ablation of atheroma and intracoronary stenting. Stenting has clearly become the dominant technique. The mostly widely used form of atherectomy involved the use of a windowed cylindrical housing compressed against the stenosis. An attached balloon was inflated against the opposite wall of the artery. Atherosclerotic plaque was then shaved from the vessel wall by advancing a rotating metal blade and debris was collected at the tip of the catheter. The luminal area was increased by the dilating effect of the device itself, inflation of the balloon, and removal of atherosclerotic material (12, 13). However there was little or no advantage seen over PTCA in early randomised trials and, in particular, restenosis rates were worse (14, 15) or similar (15). On the contrary, the first human coronary stent implantation in 1986 reported by Sigwart et al. (16) was a major advance in the field of interventional cardiology. This was achieved by the delivery of a self expanding device which acted as a scaffold within coronary arteries to treat acute vessel dissection and reduce the risk of restenosis. Their introduction helped to overcome the problem of abrupt closure seen with PTCA with resultant reduction in the need for emergency CABG (17, 18). Relative restenosis rates were also reduced by up to 20-30% in pivotal early trials compared to PTCA (19, 20), predominantly as a result of abolishing the problems related to elastic recoil and negative vascular remodelling following PTCA. More widespread approval for their use followed these trials. With the development of these other techniques, the term percutaneous coronary intervention (PCI) was eventually introduced to encompass all forms of coronary intervention.

The early stents, plus future generations of different metallic stents, without additional coatings or other means of applying pharmaceutical agents, have become collectively known as “bare metal stents” (BMS).

Despite the introduction of BMS, the rates of repeat revascularisation at one year remained relatively high at 10 to 20 percent of patients (21). This was predominantly related to neointimal proliferation within the stented segment. Neointimal proliferation can occur to a greater extent with a BMS than with PTCA, probably as a reaction to the foreign material remaining in the vessel (22). But restenosis is less because the dilation result is so much better. Although late loss is more, the acute gain is much higher, and the net gain is therefore more (Figure 1 A-B). So, research was targeted at how to get the benefits of stenting without the downside of neointimal growth. A number of different strategies were employed. These included improving stent design but also pharmacological, mainly systemic, therapies in conjunction with BMS. But the most promising was the development of drug eluting stents (DES) in the early 2000s. Safety and feasibility of this new concept, involving the use of drug coated stents with local delivery of powerful anti-proliferative drugs, was demonstrated by Sousa et al. along with remarkably low late loss (23). Pivotal trials demonstrating superiority over BMS in terms of restenosis and repeat revascularisation (24, 25) led to approval from the United States Food and Drug Administration (FDA) and widespread use. With the introduction of DES, it seemed as though there was finally an effective strategy for preventing restenosis but concerns over their long term safety were raised with higher rates of late stent thrombosis reported once dual antiplatelet therapy (DAPT) was stopped (26) (see section 1.6). The use of DAPT therapy had become

standard practice in the stenting era but only for 1 month with BMS. Calls for more prolonged DAPT use in the case of DES would potentially come at a cost of higher bleeding rates. Further research and development was therefore still required (section 1.6).

Vascular brachytherapy (VBT), introduced in the mid- late 1990s also deserves some mention. This involved the successful use of intracoronary radiation mainly to treat restenosis following PTCA or BMS implantation (27, 28). Preliminary animal studies showed that these benefits may have been mediated by apoptosis, inhibition of the first wave of cellular proliferation, and prevention of adventitial fibrosis (29). However, DES were subsequently found to be superior in treating restenosis in BMS compared to VBT and this led to a decline in its use (30, 31).

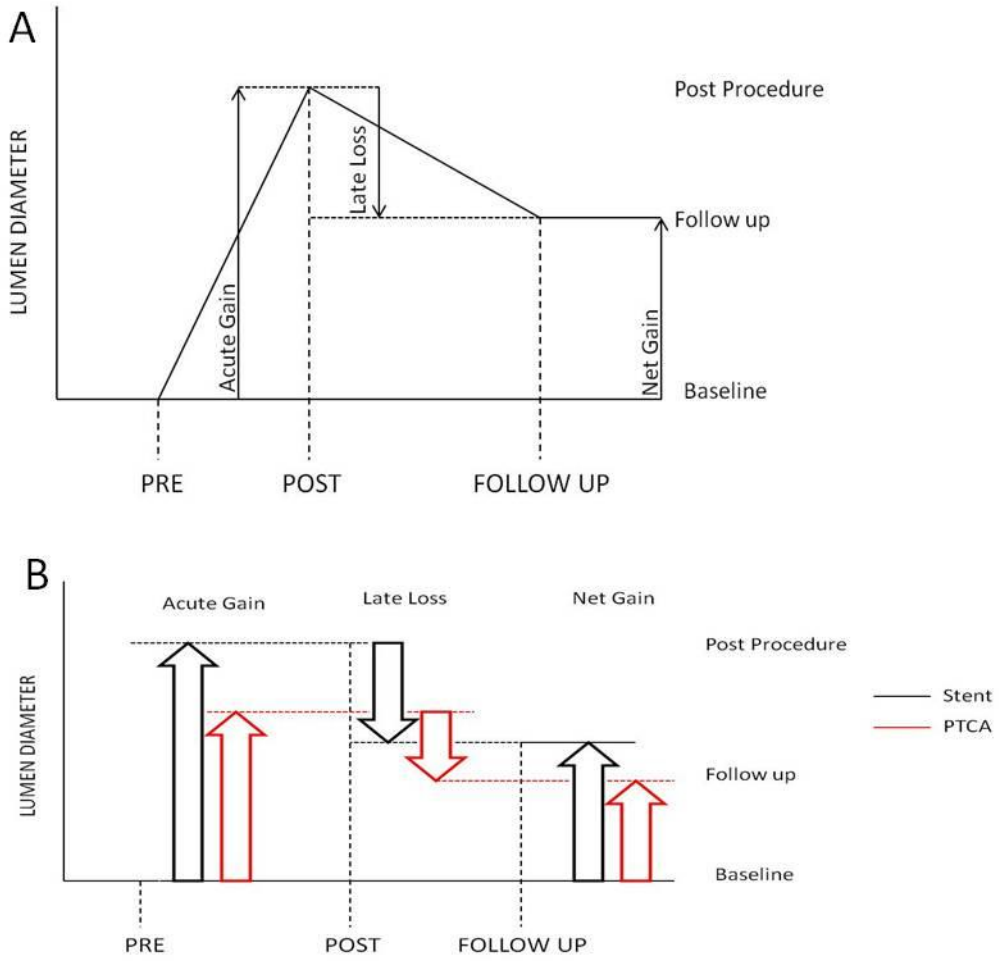


Figure 1. Diagram showing changes in luminal diameter over time after coronary intervention. A) Acute gain is the difference between the minimal luminal diameter post procedure and pre procedure. Late loss is the difference between the minimal luminal diameter post procedure and follow up and net gain is the difference between acute gain and late loss. B) Net gain is higher with stents compared to PTCA because acute gain is proportionally higher than late loss.

PTCA = Percutaneous Transluminal Coronary Angioplasty

1.2 Definitions

Restenosis has historically been defined angiographically as reduction in coronary artery lumen diameter following PCI, regardless of mechanism, but which predominantly reflects neointimal formation when stents are used. However, there are some agreed definitions that are commonly employed including:

Binary angiographic restenosis which refers to a greater than or equal to 50% reduction in the minimal luminal diameter (MLD) in the stented segment at follow up angiography (32).

Clinical restenosis which is either binary angiographic restenosis and symptoms or signs of ischaemia or, a greater than or equal to 70% reduction in the MLD in the stented segment (33) .

Although different definitions have been adopted in various scientific studies, binary angiographic restenosis is the most widely accepted with some physiologic basis. An early animal study showed that constriction of coronary arteries beyond 50% resulted in a reduction in coronary flow reserve (34). Following the widespread adoption of BMS, a group from the Mount Sinai Medical Center and the Cardiovascular Research Foundation further proposed an angiographic classification of restenosis (Table 1) (35). The clinical classification has been defined in the drug eluting stent (DES) era (Table 2) (33).

Angiographic restenosis and classification
Diameter stenosis ≥50 percent
Type I focal: ≤10 mm in length
-IA articulation or gap
-IB margin
-IC focal body
-ID multifocal
Type 2 diffuse: >10 mm intrastent
Type 3 proliferative: >10 mm extending beyond the stent margins
Type 4 total occlusion: Restenotic lesions with TIMI flow grade of 0

Table 1. Classification of restenosis. Adapted from Mehran R, Dangas G, Abizaid AS, Mintz GS, Lansky AJ, Satler LF, et al. Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. Circulation. 1999 Nov 2;100(18):1872-8.

Clinical restenosis: Assessed objectively as requirement for ischemia-driven repeat revascularization

- Diameter stenosis ≥50 percent **and** one of the following:

- Positive history of recurrent angina pectoris, presumably related to target vessel
- Objective signs of ischemia at rest (ECG changes) or during exercise test (or equivalent), presumably related to target vessel
- Abnormal results of any invasive functional diagnostic test (eg, coronary flow velocity reserve, FFR <0.80); IVUS minimum cross-sectional area <4 mm^2 (and <6.0 mm^2 for left main stem) has been found to correlate with abnormal FFR and need for subsequent TLR
- TLR with diameter stenosis ≥70 percent even in absence of the above ischemic signs or symptoms

Table 2. Clinical restenosis. Adapted from Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation. 2007 May 1;115(17):2344-51.

FFR = fractional flow reserve, IVUS= Intravascular ultrasound, TLR = target lesion revascularisation

The clinical definition also introduces the terms target lesion revascularisation (TLR), target vessel revascularisation (TVR) and target vessel failure (TVF) (21).

- TLR is defined as repeat PCI of the treated coronary segment or bypass surgery of the target vessel.
- TVR includes repeat PCI of the target vessel irrespective of the location of the stenosis.
- TVF is defined as TVR, any death, or myocardial infarction (MI) of the target vessel territory after hospital discharge.

In the earlier days of PCI, with both balloon angioplasty and stenting, there was a rough rule of halves that the clinical restenosis rate was roughly half the angiographic restenosis rate (21). So, if one group had a 30% restenosis rate you would expect about 15% to have represented with recurrent symptoms.

Quantitative coronary angiography (QCA) has been used for decades as a validated tool to assess stenosis severity (36). It involves computer assisted quantification of both disease and restenosis severity. It can be performed on-line during PCI as well as off-line with image acquisition and processing. Various software packages are available and offer different techniques including automated edge-detection and densitometry (37). The main advantage of QCA in clinical trials assessing restenosis is to provide an objective measure compared to visual assessment. This would theoretically mean freedom from observer bias and therefore minimise intra- and inter-observer variability (38, 39).Visual assessment of the severity of coronary stenoses leads to overestimation in severe lesions and underestimation in mild to moderate lesions (40).

There are many different angiographic parameters measured by QCA (Figure 2). Amongst them are the minimum luminal diameter (MLD), lesion length and

percentage diameter stenosis calculated as a percentage of the reference diameter of the artery. This is reliant on the reference vessel diameter being normal which is not always the case considering the often diffuse nature of coronary atherosclerosis or indeed neointimal proliferation in the case of restenosis. Reference diameters can also vary depending on other factors such as vasomotor tone and pharmacological interventions such as the administration of intracoronary nitrates. The MLD and its derived measurements, acute gain (post-PCI MLD minus pre-PCI MLD), late loss (MLD at follow-up minus post-PCI MLD) and net gain (acute gain minus late loss) are therefore important parameters in assessing restenosis and minimising variability (see section 1.1, Figure 1). The late loss index is the relation of late loss to acute gain: late loss index is late loss divided by acute gain.

There are other advanced imaging techniques such as intravascular ultrasound (IVUS) and more recently optical coherence tomography (OCT) that enhance visualisation of the vessel wall and also allow quantitative measurements including MLD. QCA measurements, more so with densitometry rather than edge detection methods, have been shown to correlate with IVUS following PTCA (41).

Another key concept in evaluating restenosis is the difference between in-stent and in-segment measurements (Figure 2 B). In-segment refers to the stented segment plus five millimetres proximal and distal to it. This is important because of the issue of “geometric miss”, caused by a response to barotrauma outside the stent from either the end of the stent balloon or post dilatation balloons. It is important that the stent balloon or post-dilatation

balloons do not overhang the stent too much. In order to prevent or minimise the effects of geometric miss, balloons were redesigned and the position of markers were placed relative to the shoulder of the inflated balloon.

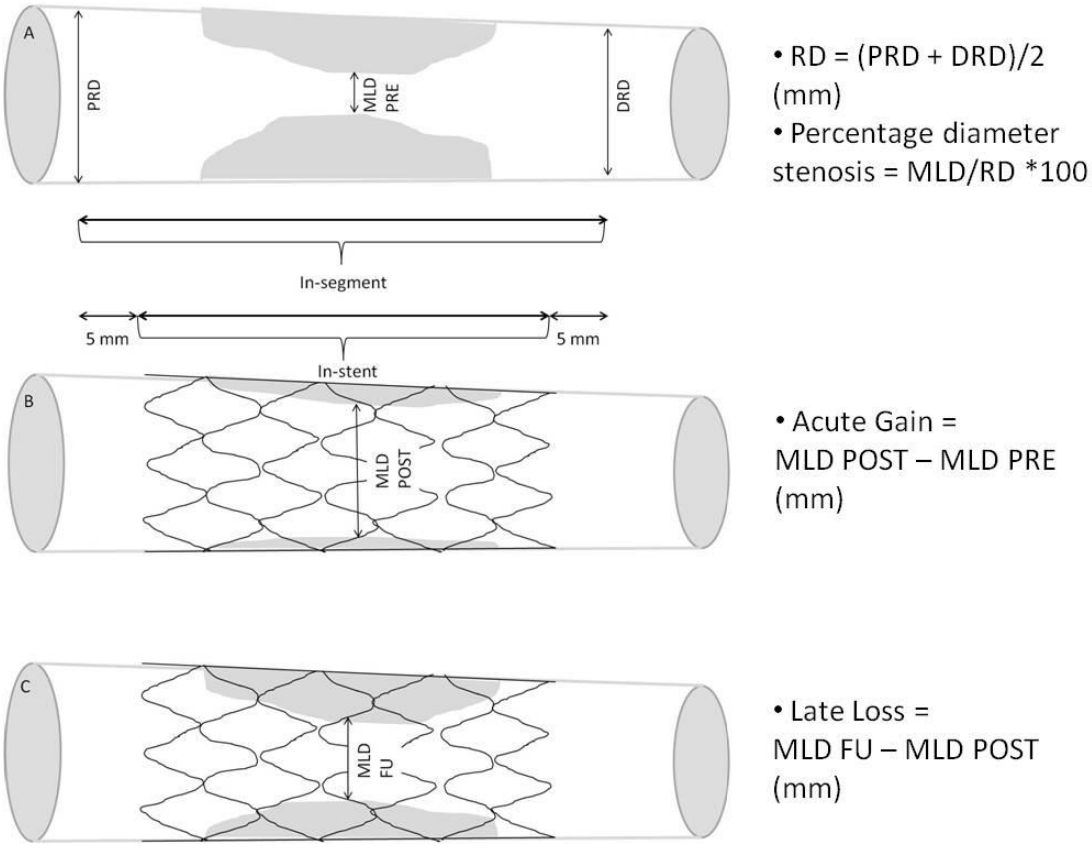


Figure 2. Diagram illustrating various parameters relating to assessing coronary stenoses in relation to PCI before, after and at follow up. A) Coronary stenosis pre-PCI, demonstrating MLD, PRD and DRD. Diameter stenosis is MLD as a percentage of the averaged RD. B) Post-PCI, in-segment measurements refer to the region within the vessel including the stent (in-stent) and 5mm proximal and distal to it. Acute gain is the difference in MLD post stenting and pre stenting. C) At follow up angiography, late loss is the difference between MLD at follow up and post stenting.

PRD = proximal reference diameter, DRD = distal reference diameter, RD = reference diameter, MLD = minimum luminal diameter, FU= follow up

1.3 Pathophysiology/mechanism of restenosis

Normal coronary arteries consist of 3 distinct layers:

1) The *intima*, or innermost layer, is a narrow layer which is bound on the luminal side by a single layer of endothelial cells and peripherally by a fenestrated sheet of elastic fibres, the *internal elastic lamina*. There is also a sub-endothelial layer comprising of various components of extracellular connective-tissue matrix including collagenous bundles and some elastin.
2) The *media*, or middle layer of the muscular artery, consists mainly of diagonally oriented smooth muscle cells (SMCs), surrounded by variable amounts of collagenous fibrils.
3) The *adventitia*, or outermost layer of the artery, consists principally of fibroblasts intermixed with SMCs loosely arranged between bundles of collagen and ground substance. It is usually divided from the media by an elastin layer, the *external elastic lamina* (very elastic and allows most of the stretch of an artery).

The most reported underlying mechanism is the response to mechanical injury resulting in neointimal formation (Figure 3). This hypothesised mechanism stemmed from earlier work looking at the inflammatory basis for atherosclerosis. Experimental work involving injury to endothelial cells using balloon catheters provided an early insight into the cellular processes

occurring after arterial injury including platelet aggregation and smooth muscle cell (SMC) proliferation (42).

Trauma to the arterial vessel wall by intracoronary stenting within the intima leads to disruption of the endothelial cell layer and actual damage to vascular endothelial cells. This triggers a remodelling process. Local deposition of platelets and fibrin mark the onset of this process (43). There is an influx of inflammatory cells including macrophages and T cells with consequent release of pro-inflammatory cytokines by these cells as well as the damaged endothelial cells. These, in turn, stimulate migration and proliferation of medial SMCs across the internal elastic lamina towards the intima. Once in the sub-endothelial space, these SMCs co-ordinate synthesis of extracellular matrix (composed of proteoglycans and collagens) which is the main component of neointima (44-49). This process is enhanced by local production of various growth factors such as transforming growth factor β and platelet derived growth factor which are thought to shift the phenotype of these smooth muscle cells such that they produce abundant extracellular matrix proteins (50). If there is excessive growth of this neointimal layer, there will be resultant loss of lumen diameter.

Another postulated mechanism for the development of neointima includes differentiation of circulating progenitor cells into SMCs capable of secreting extracellular matrix under the influence of cytokines released by endothelial cell injury and triggering growth factor production. This was based on observations from experimental studies in animals with the use of Dacron grafts that became covered with endothelial cells and vascular smooth muscle cells despite being a barrier to smooth muscle cell migration from the media

(51-53). More recently, studies have provided evidence that bone marrow derived progenitor cells can give rise to neointimal SMCs in various types of native and accelerated atherosclerotic lesions, including post-PCI restenosis (54, 55).

Cytokine release also stimulates migration of advential fibroblast cells across the external elastic lamina, through the tunica media, and across the internal elastic lamina to the intima. These migratory fibroblasts then differentiate into smooth muscle cell-like cells known as myofibroblasts with subsequent extracellular matrix secretion under the influence of pro-inflammatory cytokines and growth factors (56).

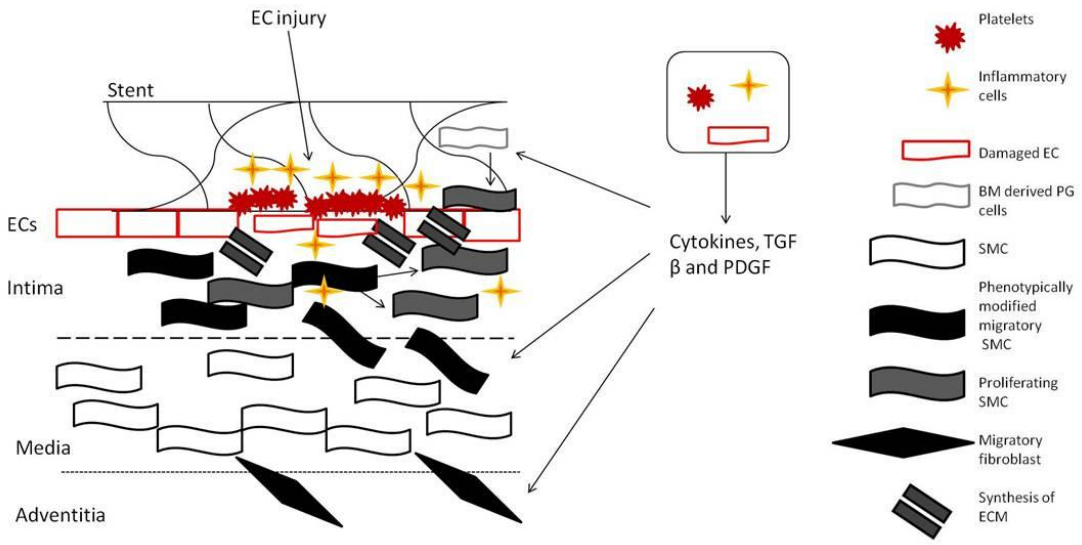


Figure 3. Diagram depicting the cellular mechanism of ISR. The migration and phenotypic modification of SMCs within the media by platelets, inflammatory cells and damaged ECs is the predominant process leading to synthesis of ECM. ECM is the predominant component of neointima responsible for ISR. Differentiation of BM derived PG cells and fibroblasts with subsequent migration into the intima are also thought to contribute to ECM.

EC = Endothelial cell, BMPGC = Bone marrow derived progenitor cells, SMC = Smooth muscle cell, ECM = Extracellular matrix, ISR = In-stent restenosis

1.4 Time course of restenosis

From post mortem and post CABG analysis of stented vessels in the BMS era, the time course of histological vascular responses to coronary stenting have been documented (Figure 4). Early (≤11 days) changes included the presence of fibrin, platelets and acute inflammatory cells such as neutrophils in association with stent struts. The severity of these changes was determined by the arterial wall-stent interface with more inflammatory cells seen if the stent was adjacent to a lipid core or injured media as compared to fibrous plaque.

Chronic inflammatory cells including lymphocytes and macrophages were present at all time points but more so late in the process (≥12 days). Neointima, which comprised of spindle-shaped mesenchymal cells (α-actin positive smooth muscle cells) within a proteoglycan matrix, was not seen in any of the sections ≤11days after stent implantation. They were seen in 45% of sections at 12-30 days and in all sections ≥30 days after stent implantation. As with the early inflammatory changes where a more severe response was seen when stent struts were adjacent to medial laceration or rupture, neointimal thickness was also greater when stent struts were adjacent to medial injury compared to fibrous plaque in those stents implanted for ≥30 days (48).

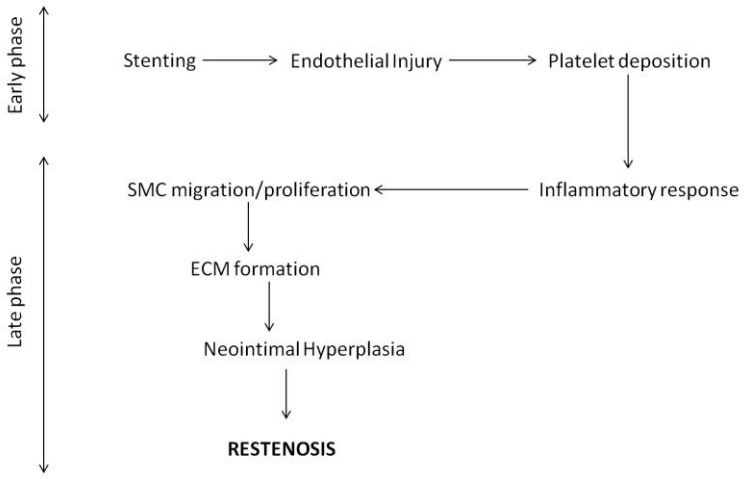


Figure 4. The time course of restenosis in bare metal stents. The early phase predominantly occurs within 11 days of stent implantation and represents the initial injury and subsequent acute inflammatory process. The late phase is usually complete by 30 days post implantation and involves the formation of extracellular matrix (ECM). Neointimal hyperplasia, in turn, is responsible for restenosis.

The processes described above were mainly investigated during the PTCA and early BMS era. Neointima was identified as a target for reducing restenosis and this led to the development of DES (section 1.6). In current practice, and with the widespread use of DES, further mechanisms can also be considered (57). These include:

- Biologic factors such as drug resistance or hypersensitivity which can be due to the stent platform, anti-restenotic drug or polymer carrying the drug.
- Mechanical factors such as stent under expansion, non-uniform stent strut distribution, stent fracture and non-uniform drug elution.

- Technical factors such as barotrauma outside the stented segment, stent gap or residual uncovered atherosclerotic plaques.

1.5 Risk factors for restenosis

A number of clinical features have been implicated in restenosis following BMS implantation. The presence of diabetes mellitus has been shown to be an important risk factor (58). Anatomic factors shown to have an increased likelihood of restenosis include small vessel diameter, long lesions, chronic total occlusions, bifurcations, ostial location, complex lesions as defined by the American Heart Association/American College of Cardiology (ACC/AHA) classification and saphenous vein graft intervention (59-62). Diabetic patients are more likely to have these types of lesions. These findings may be explained by observations from pooled analyses of BMS studies which showed that by obtaining a larger luminal diameter post stenting, the chances of developing significant restenosis are lower because this allows for more neointimal hyperplasia to develop before in-stent restenosis (ISR) occurs (63). In other words, just as with the PTCA versus stent comparison, higher acute gain results in greater net gain within the stented segment. The acute gain in lesions with the unfavourable characteristics described above is likely to be smaller than in focal lesions in large vessels. Also, lesion complexity often relates to vessel tortuosity and calcification which make it more difficult to deliver and dilate larger balloons and stents.

Following on from this, procedure and stent related factors also have an impact on ISR (section 1.9). It is more likely to occur with thicker stent struts (64), in longer stented segments (65), in multiple lesion intervention (66), in

treatment of restenotic lesions (67) and in association with mechanical complications such as stent under-expansion (68). Thicker stents may cause more stretching of the vessel resulting in a more severe inflammatory reaction leading to more neointima. As for the rest, there are likely to be multiple factors involved but increased injury and amount of foreign body material are likely to have a role.

Whilst DES have reduced restenosis, certain factors such as patients with diabetes mellitus, restenotic lesions, saphenous venous graft disease and bifurcations remain problematic (69).

1.6 Bare metal stents versus drug eluting stents

Drug eluting stents (DES) were developed to reduce restenosis by inhibiting neointimal hyperplasia (70). The first generation DES comprised of a standard metallic stent, a polymer coating and an anti-restenotic drug. The most studied and clinically used first generation DES included sirolimus eluting stents (Cypher®, Cordis, Miami, FL, USA) and paclitaxel eluting stents (Taxus®, Boston Scientific, Natick, MA, USA). Sirolimus was first developed to prevent rejection of kidney transplants in the 1970s (70) . It is a macrocyclic triene antibiotic and has immunosuppressive and anti-proliferative properties, the latter making it attractive for use in preventing restenosis. It works by binding to FK506-binding protein 12 (FKBP12). FKBP12 is up-regulated in neointimal SMCs. The resultant complex inhibits the mammalian target of rapamycin (mTOR), which results in up-regulation of cyclin-dependent kinase inhibitor p27Kip1. This blocks the migration and proliferation of SMCs by arresting the cell cycle in the gap 1 (G1) phase (70).

Sirolimus therefore has predominantly a cytostatic effect. Conversely, paclitaxel has a cytotoxic effect. Also developed in the 1970s and used as an anti-tumour drug, it binds to the β-tubulin subunit of microtubules, inhibiting the disassembly of microtubules and thereby arresting cell replication in the G0–G1 and mitotic phases of the cycle of SMCs (70).

Following the successful introduction of first generation DES, there was widespread uptake of their use. With regards to efficacy, DES and BMS have been compared in multiple randomised trials mostly involving first generation DES. A comprehensive meta-analysis including 38 trials (18023 patients) showed that patients treated with first generation DES had less TLR compared to BMS. The reduction in TLR overall was 70% ($p<0.0001$) with sirolimus-eluting stents (SES) and 58% ($p<0.001$) with paclitaxel-eluting stents (PES) compared to BMS (71). The risks of short- and longer-term mortality were similar. This was, however, preceded by a period of relative uncertainty driven by the simultaneous presentation of two meta-analyses at the European Society of Cardiology (ESC) annual conference in 2006. In what became known as the "ESC firestorm", the main findings from these meta-analyses were that first generation DES, in particular sirolimus eluting stents, were associated with higher rates of death and the combined end-point of death plus myocardial infarction (MI) (72, 73). Nordmann et al. demonstrated a statistically significant increase in non-cardiac mortality 2–3 years after SES implantation (72) and Camenzind et al. showed that the cumulative incidence of death or large MI was 6.3% for DES versus 3.9% for BMS ($p=0.03$) (73). This was later challenged by Serruys and Daemen. They analysed patient level data of the same cohort and widened the definition of MI to include all

MI. They found the actual rate of death or MI was 11.4% in the DES group and 10.1% in the BMS group (p=0.4) (74).

The proposed mechanism for the difference in events found by Camenzind et al. was late stent thrombosis. Delayed or incomplete endothelialisation of the stent platform, seen with DES, is a recognised substrate for stent thrombosis (75-77).This is an uncommon, yet potentially, life threatening complication. Following the "ESC firestorm" controversy, there were two important consequences. Firstly, there was a non-evidence based recommendation for prolongation of dual antiplatelet therapy by guideline writing authorities (78, 79) understanding concerns over an increased risk of bleeding associated with their prolonged use. Secondly, there was a fall in the rates of DES use.

Although we have seen the clear benefits of DES in reducing neointimal hyperplasia and also clinically driven repeat revascularisation compared to BMS, some studies using serial IVUS measurements in patients receiving first generation DES have reported a small late (2-4 years after implantation) increase in neointimal tissue (80, 81). Original studies with BMS showed that most restenosis occurred as a relatively early event, most often becoming clinically evident within the first 6 months, but up to 12 months after the procedure. Beyond this time, recurrent ischemia was more likely to be due to new or progressive disease at another site rather than restenosis. The evidence for this was illustrated in a review of 1228 patients who were followed for five years. After the first year, the annual hazard rate was 1.7 percent for target lesion events compared to 6.3 percent for non-target lesion events (82). Drug eluting stents, on the other hand, have a lesser degree of in-stent lumen loss at six to nine months (0.1 to 0.4 versus 0.8 to 1.1 mm with

BMS) (83, 84). The precise reason for this "late catch-up" with DES is unclear, but it may be related to a delayed healing response, persistent biological reaction caused by the drug soon after implantation, or a hypersensitivity reaction to durable polymer. The obvious concern here would be delayed restenosis. Subsequent studies have shown that “late late” restenosis occurs with bare metal stents as well.

The mechanism behind very late restenosis appears to be different from early restenosis. Investigations have led to an understanding of what has been termed neoatherosclerosis. This was noted in BMS by Inoue at al. who reported histology findings of BMS implants on post mortem studies of patients who had died of non-cardiac causes. They found atherosclerotic changes (neovascularisation, inflammatory cells and foam cell accumulation) as opposed to only neointimal changes within stented segments more than two years old (85). They suggested the possibility that these changes were the result of a persistent inflammatory response to the metal foreign body. Hasegawa et al. also showed necrotic core elements of atherosclerosis in directional atherectomy specimens of patients treated for restenosis of BMS implants more than 5 years old (86). Interestingly, four of the series of fourteen samples had been from patients presenting with an acute coronary syndrome (ACS). In the DES era, Nakazawa et al. identified neoatherosclerotic changes more frequently in DES (sirolimus eluting) compared to BMS (35% vs 10%, $p<0.001$, n=143) (87). They also found that the timing of these changes were different, the earliest changes being seen at four months for DES compared to 2 years with BMS.

To begin with, restenosis in BMS was generally considered to be a benign process with most patients presenting in a stable manner with symptoms of recurrent ischaemia but it is now known that up to a third of patients can present with an ACS (88, 89). With the advent of first generation DES, restenosis rates were reduced but, as discussed above, there were concerns about delayed restenosis and stent thrombosis and all of the components of DES had been implicated. Newer strategies were needed.

One of the key new developments was the evolution of second generation DES. Their use has now superseded first generation DES use. They include everolimus-, zotarolimus- and biolimus-eluting stents. These drugs are all derivatives of sirolimus and therefore have a similar mechanism of action. Everolimus was first approved for use in advanced renal carcinoma (90) whereas zotarolimus and biolimus were specifically developed to prevent the proliferation of smooth muscle and other cell types seen with restenosis (91, 92). The newer DES also benefit from improvements in stent platform, including different materials and thinner stent struts, and polymer design, including the use of more biocompatible materials. Beyond these, there have also been developments in biodegradable or bioresorbable stents (93). However, given that some of the downside of DES might be due to these cytostatic anti-proliferative drugs there was also revived interest in other biological targets. One of these was steroids, more specifically glucocorticoids.

1.7 Glucocorticoids

Glucocorticoids, of which cortisol is the major type in humans, are a class of steroid hormones that have a variety of effects but are mainly involved in regulation of metabolic and defence responses. They are produced in the adrenal cortex and are regulated by a process of negative feedback within the hypothalamic pituitary adrenal (HPA) axis. There is a clear circadian pattern with peak levels in the early morning. Most of the cortisol secreted into the blood is bound to corticosteroid-binding globulin and albumin with only 5-10% of the unbound form available to interact with receptors which are the principle mechanism for their interaction with cells. Metabolic inactivation of glucocorticoids occurs predominantly in the liver, and also in the kidney, with inactive metabolites excreted in the urine (94).

1.7.1 Mechanism of anti-inflammatory action

Activation of the HPA axis in response to stress such as sepsis, trauma or tissue ischaemia results in an increase in cortisol release (95). Cortisol enters cells passively by diffusing across the cellular membrane and binding to the glucocorticoid receptor (GR) resulting in a cortisol-GR complex. It can then mediate its effects via three mechanisms. Firstly, the cortisol-GR complex is translocated into the nucleus and binds to glucocorticoid response elements in target genes. This leads to alterations (induction or inhibition) in transcription. Secondly, the cortisol-GR receptor complex can interact with other transcription factors, such as nuclear factor κB and thus regulate other glucocorticoid response elements. Thirdly, via non-genomic pathways involving glucocorticoid signalling through membrane associated receptors

and second messengers. Inflammation is inhibited by all of these pathways (96) (Figure 5).

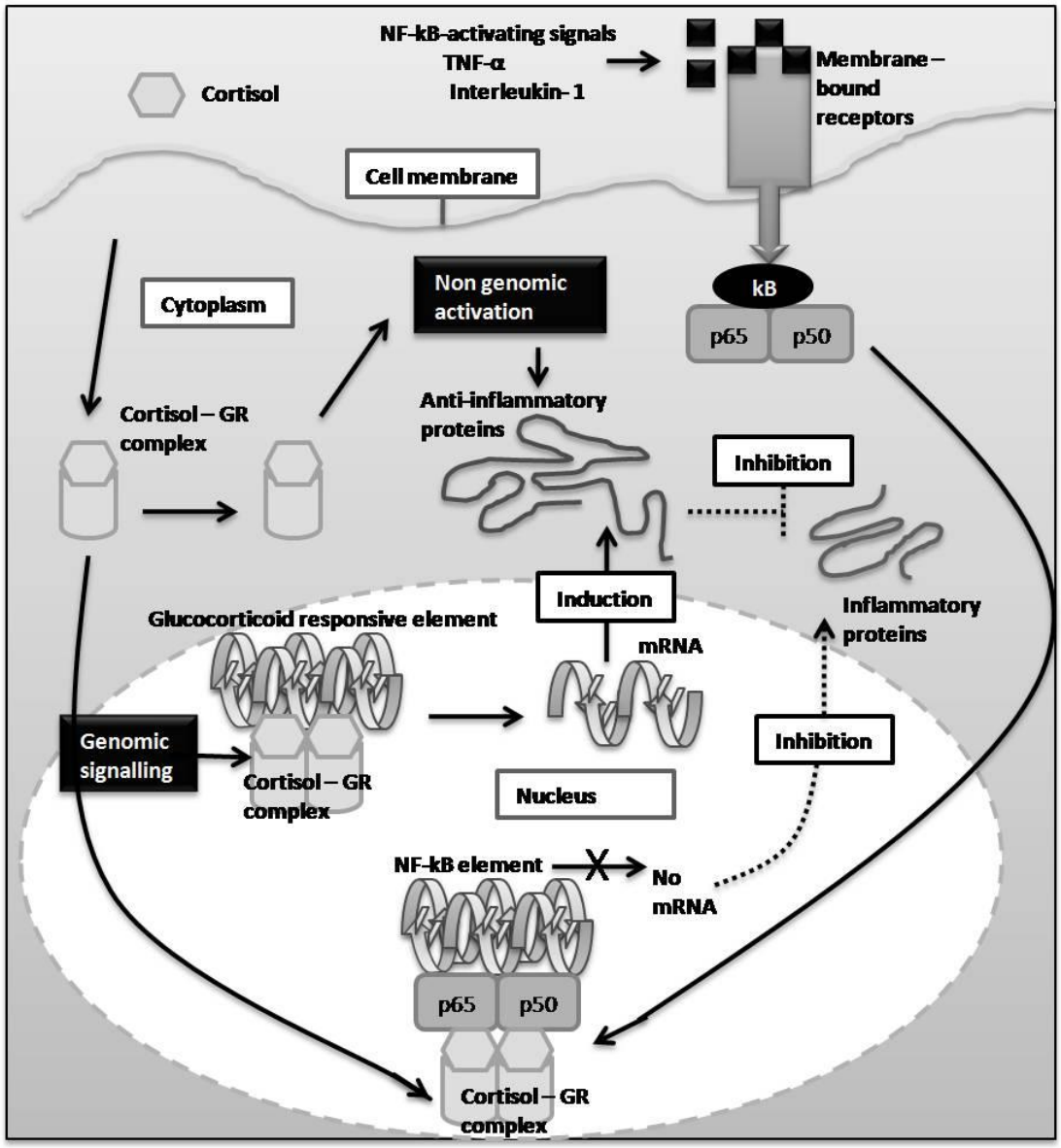


Figure 5. Mechanism of anti-inflammatory action of glucocorticoids shown in an endothelial cell. Adapted from Rhen T, Cidlowski JA. Anti-inflammatory action of glucocorticoids--new mechanisms for old drugs. N Engl J Med. 2005 Oct 20;353(16):1711-23.

Cortisol can inhibit inflammatory proteins by genomic and non-genomic pathways. Cortisol binds to intracellular glucocorticoid receptors (GR) resulting in a cortisol-GR complex. The cortisol-GR complexes enter the nucleus and bind to glucocorticoid responsive elements or other relevant transcription factors such as NF-kB (activated by cytokines in response to stress via membrane bound proteins) leading to induction or inhibition of transcription (synthesis of mRNA) (genomic signalling). The cortisol-GR complexes mediate their ant-inflammatory effects via second messengers within the cytosol as opposed to translocation into the nucleus (non-genomic activation).

NF kB = Nuclear Factor kB, TNF-α = Tumour Necrosis Factor α, cortisol-GR = cortisol - glucocorticoid receptor, mRNA = messenger RNA

1.7.2 Regulation of glucocorticoids and their cardiovascular effects

Glucocorticoids also interact with mineralocorticoid receptors (MR) within the cell. GRs are expressed in all tissues whereas MRs are expressed in selected tissues only. Mineralocorticoids, principally aldosterone, are another group of steroid hormones that are primarily involved in regulation of electrolyte and water balance. Cortisol is present in much higher concentrations than aldosterone yet there is a difference in selectivity shown by MRs between cortisol and aldosterone (94).

This difference in affinity is explained by tissue specific differences in expression of the enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD). Two isozymes of 11β-HSD, type 1 and type 2 have been identified, both of which are microsomal enzymes of the short-chain alcohol dehydrogenase

superfamily. 11β-HSD type 1 (11β-HSD1) is a low affinity nicotinamide adenine dinucleotide phosphate (NADPH)-dependent enzyme which acts predominantly as a reductase converting cortisone to cortisol. Dehydrogenase activity is not usually seen in intact cells. 11β-HSD1 is widely expressed in many glucocorticoid-target tissues including liver, lung, adipose tissue, brain, vascular smooth muscle, skeletal muscle, anterior pituitary, gonads and adrenal cortex where it amplifies local glucocorticoid concentrations (97, 98).

In contrast to 11β-HSD1, 11β-HSD2 is a high affinity nicotinamide adenine dinucleotide (NAD) dependent dehydrogenase isoenzyme. It converts active glucocorticoids into inactive 11-ketosteroids such as cortisone. It is expressed mainly in mineralocorticoid target tissues including kidney (distal nephron), sweat glands, salivary glands and colon where it protects MRs from occupation by glucocorticoids (97).

This understanding of where glucocorticoids exert their influence helps to explain the main actions of glucocorticoids mediated by GR stimulation. The ubiquitous expression of GR allows glucocorticoids to have different functions. They are important in the regulation of carbohydrate and protein metabolism. Glucocorticoids are also required for blood pressure maintenance although the mechanisms involved are complex and incompletely understood (99). They also have anti-inflammatory and immunosuppressive effects and this has been widely exploited from a pharmacological perspective (96). Table 3 below illustrates the heterogeneity of glucocorticoid action on the cardiovascular system.

Site of action	Via glucocorticoid receptors	Via mineralocorticoid receptors
Vascular smooth muscle	↑contractility e.g. to noradrenaline	↑perivascular inflammation
	↓proliferation	↕vasoconstriction
	↓migration	
Endothelial cell	↓endothelium-dependent vasodilatation	
	↓angiogenesis	
Myocardium		↑fibrosis
Macrophage	↕cytokines	
	↑apoptosis	
	↓phagocytosis of apoptotic neutrophils	

Table 3. Cardiovascular effects of glucocorticoids. Adapted from Walker BR. Glucocorticoids and cardiovascular disease. Eur J Endocrinol. 2007 Nov;157(5):545-59.

1.7.3 Rationale for glucocorticoid use in restenosis

Glucocorticoids play a key role in the response to stress, including following sepsis, trauma, starvation and tissue injury/ischaemia (95). Inflammation as a result of arterial injury with resultant SMC proliferation is the most widely accepted mechanism for restenosis, especially with stenting. There are a plethora of studies implicating pro-inflammatory mediators such as cytokines or chemokines in the pathogenesis of neointimal formation and restenosis and

this further substantiates the relevance for an inflammatory component. It is not surprising, therefore, that glucocorticoids, one of the most well-known and used anti-inflammatory agents, represented an attractive option to provide a crucial ‘brake’ on the innate inflammatory mechanisms that are associated with restenosis. They also have immunosuppressive and anti-proliferative effects which could be utilised to inhibit smooth muscle cell proliferation (100, 101).

These mechanisms of glucocorticoid action have been described and broadly speaking involve transcriptional regulation of the genes associated with these processes (102). The anti-inflammatory effects of glucocorticoids can be attributed to reduction of tumour necrosis factor (TNF)-α production, nuclear factor (NF)-kB inhibition, inhibition of certain chemokines and interactions with inflammatory cell recruitment (102). TNF-α is an inflammatory cytokine produced by macrophages/monocytes during acute inflammation responsible for a diverse range of signalling events (103). Dexamethasone has been shown to interfere with the production of TNF-α in endotoxin-sensitive mice (104). NF- kB is a protein complex controlling the transcription of DNA in response to inflammation amongst other actions and is chronically active in atherosclerosis (105). Interference of the activated glucocorticoid receptor with the transactivation potential of the NF-kB p65 subunit leads to the reduction of gene activation by dexamethasone (106). These observations provide an explanation of how dexamethasone inhibits the cytokine induced transcription and mRNA destabilisation of inflammatory genes. As a result, there are reduced levels of a number of gene products potentially implicated in restenosis such as the chemokines monocyte chemotactic-activating factor

(107), IL-8 (108), endothelial ICAM-1, E-selectin, and VCAM-1 (109-111). Dexamethasone has also been described to inhibit cytokine-stimulated mRNA expression and protein release of another chemokine, RANTES, in epithelial cells and T lymphocytes (112, 113), and inhibition of this has been shown to attenuate neointimal proliferation in mice (114).

Dexamethasone has also been found to prevent the expression and release of tissue factor which induces a procoagulant response in damaged endothelial cells and mononuclear cells either directly or to cytokines indicating that it may also ameliorate endothelial dysfunction in the aftermath of the barotrauma of balloon injury (115, 116).

In addition to these anti-inflammatory mechanisms, apoptosis has also been implicated with restenosis. Following stretch injury by angioplasty, SMCs closest to the region of injury have been shown to undergo apoptosis in rats (117). The surviving SMCs then migrate and proliferate through phenotypic modulation as a response to this injury leading to neointima (118). An inhibition of NF-kB mobilization and NF-kB-dependent expression of anti-apoptotic proteins (inhibitor of apoptosis protein family) has been demonstrated to sensitise proliferating SMCs for the induction of apoptosis, thereby contributing to SMC stasis (119). This could serve as an alternative mechanism linking anti-inflammatory and pro-apoptotic and growth-limiting effects (120) by which an inhibition of NF-kB transactivation with glucocorticoids could contribute to prevention of restenosis.

In general terms, glucocorticoids affect key processes involved in neointimal formation which, when excessive, leads to restenosis. Their anti-inflammatory

properties allow them to affect the distribution and function of all types of leucocytes and, in particular, to inhibit monocytes and macrophages thereby targeting the early phase inflammation leading to restenosis. They may also have an anti-proliferative role by targeting proliferating SMCs affecting the later stages of the restenotic process. This may, however, be dependent on the delivery, dose and time-course of steroid release.

1.7.4 Local vs. systemic delivery and clinical trials

The discussion above has focused predominantly on the systemic effect of glucocorticoids mainly in the context of restenosis. Table three summarised the diverse actions of glucocorticoids on the cardiovascular system. Whilst their local anti-inflammatory properties are attractive in the battle against restenosis, could these be offset by adverse systemic effects?

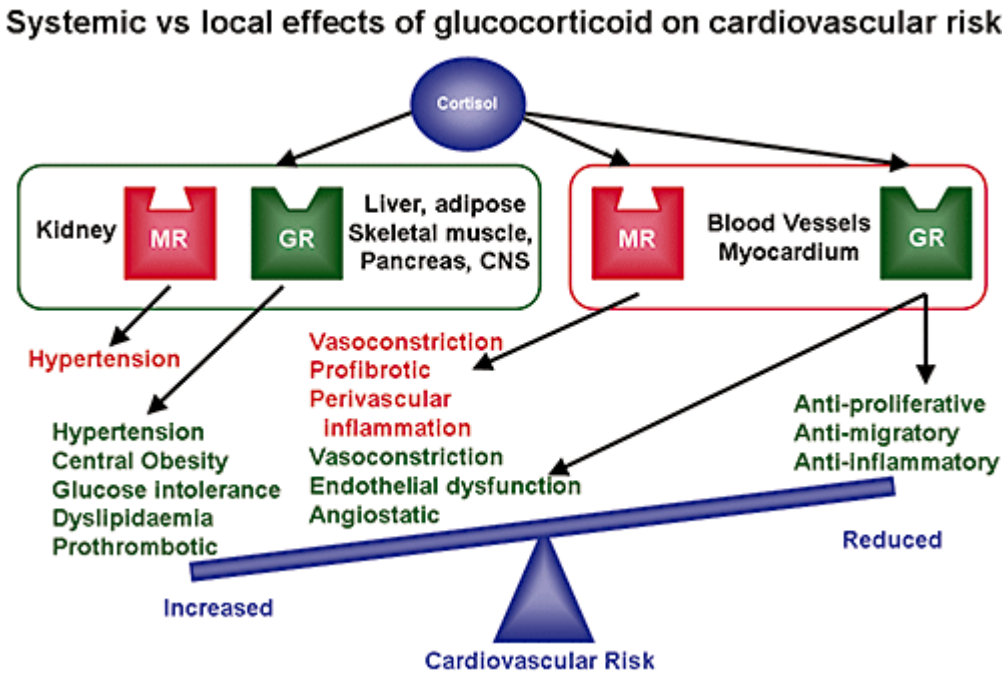


Figure 6. Systemic vs. local effects of glucocorticoids on the cardiovascular system. Systemic actions of glucocorticoids are associated with increased cardiovascular risk and are likely to promote cardiovascular disease development. Local effects on cells of the cardiovascular system may be mediated by glucocorticoid (GR) and/or mineralocorticoid (MR) receptors and could be predicted either to promote or oppose lesion development. Reproduced with permission from Hadoke PW, Iqbal J, Walker BR. Therapeutic manipulation of glucocorticoid metabolism in cardiovascular disease. Br J Pharmacol. 2009 Mar;156(5):689-712.

This question is illustrated (Figure 6) and demonstrates the interplay between glucocorticoid effects on GRs and MRs. For glucocorticoids to be beneficial, the anti-proliferative, anti-migratory and anti-inflammatory effects have to be greater in the blood vessels and myocardium. However, their use to prevent restenosis in humans has received limited investigation with variable results.

Synthetic compounds have potentially advantageous properties compared with endogenous glucocorticoid (cortisol) and therefore attempts have been made to utilise these to tip the balance in favour of preventing restenosis. For example, prednisolone and methylprednisolone have higher selectivity for GR than cortisol (3-8 fold) and longer bioavailability (biological half-life 16-40 hours compared with 2-8 hours for cortisol). Other compounds such as dexamethasone and betamethasone have even better selectivity (25–80 times) and longer biological half-lives (36–54 h) (121).

With regards to systemic therapy, two general approaches have been investigated. Three groups have studied the administration of methylprednisolone. These studies failed to identify a benefit in reducing the angiographic restenosis rate (Table 4) (122-124). Two of these studies, by Stone et al. and the M-HEART group, were conducted in patients undergoing balloon angioplasty alone. The process of restenosis following balloon angioplasty differs from that of in-stent restenosis as in addition to neointimal proliferation there is also elastic coil and negative remodelling and glucocorticoids may have little or no impact on these. The third study involving stent insertion was limited in several respects. Firstly it used single pulsed methylprednisolone the day of the procedure and, as such, patients received a relatively small total dose of corticosteroid. The study was terminated early as interim analysis failed to show a prominent impact of corticosteroids on in-stent re-stenosis. Other limitations include incomplete angiographic follow-up and the selective population studied. Patients with type C lesions (most complex lesions) were excluded from the study and only 12% of patients enrolled had hyperlipidaemia. These trials did not demonstrate efficacy of a

pulsed approach although there were also no significant adverse systemic effects reported.

Trial	Year	Patients randomly assigned	Repeat angiogram (%)	Restenosis rates (study vs. control)	Dosing
Stone et al(122) PTCA only	1989	102	53	36 % vs. 40% (p=NS)	Methylprednisolone 125 mg IM × 2 doses, then prednisone 60 mg PO od × 7 days
M-HEART(123) PTCA only	1990	915	74	40% vs. 39 % (p=0.78)	1000 mg Methylprednisolone IV × 1 dose
Lee et al(124) BMS	1998	140	91	17.5% vs 18.8% (p=0.85)	1000 mg Methylprednisolone IV × 1 dose

Table 4. Early randomized trials of glucocorticoids to prevent restenosis involving the use of pulsed doses of methylprednisolone.

NS, Not significant; PTCA, percutaneous transluminal coronary angioplasty; BMS, bare metal stent;

IM, Intramuscularly; *PO,* bymouth; *od,* daily; *IV,* intravenously; *M-HEART,* Multi-Hospital Eastern Atlantic Restenosis Trial.

The second approach has involved the post-procedural administration of oral prednisone. The IMPRESS study has shown that 45-days of oral prednisone in patients with elevated post-procedural C reactive protein (CRP) levels (CRP>0.5mg/dl at 3 days post procedure) but normal pre-procedural CRP levels reduces the absolute in-stent re-stenosis rate from 33% to 7% at 6 months (125). The dose of oral prednisone used was based on the immunosuppressive protocol utilised for heart transplantation. This study also has limitations. Diabetic patients were excluded, the study population was highly selected with only 15% of all patients referred for percutaneous coronary intervention included and only 15% of their patients were receiving lipid lowering medication. This approach is also problematic from a logistic point of view. At the time of PCI, an operator needs to decide which stent type to give to a patient. If the only choice was a BMS, then CRP could be measured on day 3 and glucocorticoids prescribed accordingly, knowing that this might reduce the restenosis rate of at least this cohort. However, the majority of the population treated would not be eligible for the potential protective effects of glucocorticoids. Given that there is now a choice between a BMS and a DES, mainly on grounds of either perceived low probability of restenosis with a BMS, or on the desire for a short course of DAPT (eg in cases where early surgery for a co-existing condition is needed, or in those at high bleeding risk), then it is impossible to pre-emptively insert a BMS in the hope that the CRP will be high 3 days later.

Approaches involving the use of local delivery of glucocorticoid therapy have been employed more sparingly. In a way, they represent the best way to overcome the limitations associated with systemic glucocorticoid therapy and could potentially be an ideal solution to the question posed earlier. A small pilot observational study included 24 patients with high risk lesions (AHA/ACC Type C). Twenty one patients (in three patients the catheter did not cross the lesion) had local delivery of methylprednisolone acetate via a catheter based delivery system before elective BMS implantation. They had a restenosis rate of 39% and did not show any reduction in restenosis compared to matched controls (126). Another approach was employed in a first-in-human multi-centre pilot trial with encouraging results (n=71). In the Study of anti-+restenosis with the Biodivsysio dexamethasone eluting stent (STRIDE), a dexamethasone eluting stent which consisted of a BMS (BiodivYsio Matrix Lo, Abbott, USA) with a phosphorylcholine coating that was firstly bathed in dexamethasone and then dried was investigated. The binary restenosis rate was 13.3% and late loss was 0.45mm in the 60 patients with angiographic follow up. Diabetic patients were not included and maximum stent length was 18mm(127).

In contrast, a further pilot study investigating the use of the same high dose dexamethasone-eluting stents failed to show a reduction in restenosis. In this observational study of 30 patients (87% had a follow up angiogram) binary restenosis was observed in 8 lesions (31%) and late loss was 0.96mm which was similar to a comparable bare metal stent platform. Based on these disappointing results plans for a larger, more definitive study were abandoned by this group (128).

It is likely that despite a more targeted approach of the GR with these local delivery systems there remains the risk that activation of the GR in the vessel may induce other changes within the vessel which offset any benefit of conventional anti-inflammatory effects. Some of these effects include increasing local angiotensin II (129) and endothelin-1 generation (130) or by decreasing endothelial nitric oxide generation(131) which can be detrimental by stimulating smooth muscle cell migration and proliferation.

To summarise, clinical trials on the use of systemic pulse applications after balloon angioplasty and stent implantation have been performed and failed to show a benefit. Systemic pulse application followed by a short period of glucocorticoid administration has been performed after balloon angioplasty also with disappointing results. In these studies, the failure to reduce restenosis could in part be attributed to an insufficient local effect, as well as a potentially reduced effect of a pulse application. Local delivery systems have had mixed results in suppression of the restenotic process in pilot studies and potential explanations are outlined above. The only convincing positive signal of glucocorticoid use in this area has been with systemic treatment with prednisone. This has been found to be effective in reducing restenosis and clinical events after stent implantation albeit in selected patients with elevated C-reactive protein a few days after stenting who then had a prolonged course of steroid. It is therefore also possible that the previous approaches did not sufficiently cover the period of maximal inflammation following stenting.

These findings have to be looked at in the context of the process and timing of restenosis in BMS (see sections 1.3 and 1.4). The relevant merits of glucocorticoid therapy to prevent restenosis (sections 1.7.2 and 1.7.3) have

unfortunately not been realised in the majority of trials discussed above. The methodology employed in these trials may help to explain their results. One important consideration is the dose of glucocorticoid required. With regards to anti-inflammatory activity, the relative potencies of commonly used systemic glucocorticoids compared to hydrocortisone are summarised (Table 5). The hydrocortisone dose is roughly based on a physiological dose when used in patients with adrenal insufficiency (132). Ideally the dose used would have to be at higher than physiological levels whilst trying to avoid some of the complications of prolonged use. In the two studies addressing glucocorticoid use to prevent restenosis in BMS, the doses appear to be sufficient (Lee et al., 1000mg methylprednisolone and IMPRESS, a reducing regimen of 1mg/kg for the first 10 days, 0.5mg/kg from day 11 to 30 and 0.25mg/kg from day 31 to 45). The timing, however, is more relevant. The pathology of restenosis in BMS begins early after PCI and continues for up to 30 days post procedure. Lee et al. utilised only a single pulsed dose of methylprednisolone. They did not therefore cover the entire period. In the case of IMPRESS, treatment designed to cover the entire period only commenced three days after the procedure in a select group of patients. There was, therefore, a need for a more inclusive trial of glucocorticoids starting pre-PCI but extending to cover the majority of the period of inflammation.

	Equivalent doses* (mg)	Relative anti-inflammatory activity	Duration of action (hours)
Hydrocortisone (cortisol)	20	1	8 -12
Prednisone	5	4	12-36
Prednisolone	5	4	12-36
Methylprednisolone	4	5	12-36
Dexamethasone	0.75	30	36-72

Table 5. Relative potencies of some commonly used glucocorticoids.

* Equivalent anti-inflammatory dose shown is for oral or intravenous (IV) administration.

Data from :

Schimmer BP, Parker KL. Adrenocorticotropic hormone; adrenocortical steroids and their synthetic analogs; inhibitors of the synthesis and actions of adrenocortical hormones. In: The Pharmacological Basis of Therapeutics, 11th ed, Brunton LL, Lazo JS, Parker KL (Eds), McGraw Hill, NY. p.1587. Copyright © 2006.

Donohoue PA. The adrenal gland and its disorders. Kappy MS, Allen DB, Geffner ME (Eds), Charles C Thomas, Springfield, IL. p.403. Copyright © 2005 Charles C Thomas, Publisher, Ltd.

1.8 Role of CRP

As described earlier, inflammation is one of the predominant processes in restenosis following stent implantation. Cytokines such as interleukin (IL)-1 and IL-6, secreted by activated macrophages, for example in response to arterial injury, are powerful stimuli for smooth muscle cell proliferation and hepatocyte production of a series of acute-phase proteins including C-reactive protein (CRP) (133, 134). CRP secretion starts four to six hours after the stimulus, duplicates every eight hours, and peaks within 36 to 50 hours. CRP has a plasma half-life of 19 hours (135). These properties led to studies on the role of plasma levels of CRP after PCI as a marker of the intensity of the inflammatory reaction responsible for neointimal proliferation and subsequent restenosis. There was also interest in using CRP to assess cardiovascular risk in the context of atherosclerosis (136) which, at least in part, shares a common inflammatory basis.

In one of the early studies investigating this issue in coronary stenting, of 81 consecutive patients with stable angina, 71% had elevated CRP levels 72 hours following the procedure. Only these patients had adverse cardiovascular events during 12 month follow up, one death due to cardiovascular causes and 12 patients (17%) had recurrent symptoms requiring repeat revascularisation for ISR. The remaining 29% whose CRP levels had normalised had no events. The investigators excluded five patients with elevated cardiac biomarkers (creatine kinase (CK), CK-MB or troponin I) post procedure. Based on this, they concluded that persistently elevated CRP

levels were not related to peri-procedural myocardial ischaemia and that this must be a consequence of a more intense inflammatory reaction (137).

Two further studies also investigated the impact of elevated CRP levels on restenosis. However, they were interested in the effect of elevated pre-procedural levels. Firstly, in patients treated with PTCA, Buffon et al. showed that after multivariate analysis in their study of 121 patients including patients with stable and unstable angina, elevated pre-procedural CRP levels were an independent predictor of clinical restenosis at 1 year (relative risk (RR) 6.2, 95% confidence intervals (CI) 2.0-18.7, p=0.001 for comparison between the group in the highest and the lowest tertile of CRP levels and RR 4.5, 95% CI 1.5-13.4, p=0.005 for comparison between the group in the middle and the lowest tertile of CRP levels) (138). Similarly, Walter et al. showed that there was a higher rate of angiographic binary restenosis after stent implantation at 6 months for 229 of 276 patients who had repeat angiography after multivariate logistic regression analysis (RR 3.6, 95% CI 1.7-7.7, $p<0.001$) for patients with pre-procedural CRP levels in the highest tertile compared to the lowest (139). This led the authors to conclude that patients with baseline low grade inflammation is an independent predictor of restenosis and therefore anti-inflammatory therapies could be of potential benefit in improving outcomes.

Further evidence for the association of CRP with ISR comes from a small study using immuno-histochemical staining for CRP. Twelve consecutive patients undergoing angiography three to 10 months after their initial procedure and found to have restenosis were included. Atherectomy samples were obtained from them. Half of the patients had atherectomy performed and

half had BMS implantation as their first procedure. Exclusion criteria included acute or recent myocardial infarction, unstable angina pectoris, uncontrolled hypertension, peripheral vascular disease, heart failure, or co-existent conditions likely to be associated with an acute-phase inflammatory response. The only differences between the two groups was that the atherectomy group did not get the antiplatelet agent ticlopidine and the reference vessel diameter was larger in the atherectomy group. The patients who had stenting as their initial procedure demonstrated more staining for CRP and macrophages than those who had atherectomy performed (140).

The studies described above have largely shown a positive association for CRP with restenosis. However two studies found that raised CRP did not predict restenosis. In one study with 75 patients who underwent directional atherectomy, 58 (77%) had elevated serum levels of CRP (>0.5 mg/dl). Of these, 16 (27.5%) developed binary angiographic restenosis whilst 7 (41%) of the 17 patients with normal serum CRP levels developed restenosis. The difference was not statistically significant leading the authors to conclude that there was no correlation between elevated serum CRP levels and restenosis (141). Another larger study of 415 patients, also observational in design, included patients who underwent PTCA alone and stenting. The reported endpoint was clinical restenosis defined as repeat revascularisation rather than binary angiographic restenosis. The participants were grouped into three tertiles of CRP values and the ranges of CRP concentrations corresponding to these tertiles were: 1.06 mg/dL, 1.07 to 1.78 mg/dL, and 1.79 mg/dL for the first, second, and third tertiles respectively with similar numbers in each group. Restenosis rates were lower with increasing tertiles 18%,13% and 10%

respectively (OR 0.7, 95%CI 0.5-0.96,p=0.03). After adjustment for other confounding factors this trend was not significant (p=0.1) (142).

As PCI with BMS became the dominant strategy, more studies assessing the role of CRP in predicting restenosis emerged. A meta-analysis including nine trials enrolling 2747 patients from 2000-2006 showed that higher pre-procedural CRP levels were a significant predictor of angiographic restenosis (OR 1.59, 95% confidence interval 1.21-2.07, p=0.001). There was heterogeneity (χ^2 14.47, p=0.07;I^2=44.7%) and publication bias was also detected (p=0.01, Egger's test). In particular, a mixture of different CRP assays were used and three did not use highly sensitive CRP as opposed to the others that did. CRP threshold values were also defined differently. CRP was around 3 mg/l in three studies, 5 mg/l in four studies, and 6.98 and 10 mg/l in one study. The study populations in the different studies were also diverse in terms of clinical syndrome. In the largest study with 834 patients, only patients with stable angina were recruited whilst in the other eight, the majority of patients had acute coronary syndromes.

So far the role of CRP in the context of restenosis has been that of a biomarker. Whilst it is true that CRP is a consequence of an inflammatory stimulus, there is also evidence to suggest that CRP has pro-inflammatory effects of its own. In vitro experiments with monocytes have shown that CRP induces the production of inflammatory cytokines IL-1, IL-6, IL-8 and TNF-α (143, 144). In endothelial cells, this is less certain. CRP has been shown to promote endothelin-1, IL-6 (145) and activate NF-kB signalling (146) in vitro. But these findings have been questioned because the CRP assays used in

these studies were contaminated with sodium azide which was found to activate endothelial cells (147).

Glucocorticoids have anti-inflammatory effects targeting some of the cytokines and signalling pathways described above (see sections 1.7.2 and 1.7.3). In addition to directly altering the response to inflammation following stenting, they may also therefore be able to affect the pro-inflammatory effects of CRP when used at pharmacological doses. Unfortunately, the studies assessing the role of CRP in restenosis were not randomised trials. Furthermore, they did not demonstrate a fall in CRP associated with glucocorticoid use.

Glucocorticoids have been shown to decrease CRP levels in other cardiovascular contexts. An inflammatory basis for atrial fibrillation (AF) has been suggested and therefore patients with a first detected episode of symptomatic persistent AF were randomised to 16mg methylprednisolone for 4 weeks followed by a tapering dose to stop at 4 months or placebo (148). Patients with AF secondary to a precipitating condition such as acute myocardial infarction or unstable angina, cardiac surgery, acute pericarditis or myocarditis, thyrotoxicosis, or acute pulmonary disease and patients with inflammatory or neoplastic conditions were excluded. CRP levels were similar at baseline in both groups. At one month follow up, CRP levels were on average 80% lower in the methylprednisolone group. They also had less recurrence of AF. In another study, 80 patients undergoing elective CABG were randomised to either glucocorticoid therapy (single dose of intravenous methylprednisolone) or placebo to see if the latter would attenuate the inflammatory consequences of cardiopulmonary bypass. IL-6, IL-8 and TNF-α levels were all significantly lower in the methylprednisolone group. CRP levels

were also significantly less at 24 and 72 hours but similar at seven days (149). In healthy volunteers, with no concurrent inflammatory conditions and in the context of normal baseline values, dexamethasone has also been shown to lower CRP (150).

The evidence presented here does not provide definitive evidence for an association between raised CRP levels and restenosis. There is however potential, perhaps by association rather than causation, that it can help to determine which patients are most likely to benefit from aggressive anti-inflammatory strategies such as the use of glucocorticoids. The evidence for benefit for such a strategy has already been described above with the results of the IMPRESS study.

1.9 The influence of bare metal stents on restenosis

Intracoronary stents were first implanted in humans by Puel and Sigwart in March 1986 (16). The original stent they employed was a stainless-steel multifilament, self-expanding stent and had what they described as "an innovative instrument for placing it" (Medinvent SA, Lausanne, Switzerland). In 12 of the 19 patients, in whom coronary stents were implanted with three to six month angiographic follow up, there was no significant luminal narrowing within the stents. This pioneering study represented a significant advance in the battle against restenosis as compared to PTCA. With greater uptake of this technology it became apparent that although better than PTCA, restenosis rates remained at an unsatisfactory level. Therefore, in addition to pharmacological strategies, another area of focus was stent design and

material. An early experimental study in rabbits showed that changing stent strut configurations reduced vascular injury by 42% (151).

The ideal stents should be flexible, trackable, visible and biocompatible. The first two properties are dependent on stent design whilst the latter two rely on stent material. It follows therefore that BMSs can be classified in different ways:

- By mechanism of action (section 1.9.2).

To begin with, BMS were available as either self-expanding or balloon expandable (152-154).

- By design (section 1.9.3).

Coil stents characterised by metallic wires or strips formed into a circular coil shape.

Mesh stents consisting of wires wound together in a meshwork, forming a tube.

Slotted tube stents made from tubes of metal from which a stent design was laser cut (155).

- By materials (section 1.9.3)

Stainless steel, platinum–iridium alloy, tantalum, nitinol, cobalt–chromium alloy, titanium, pure iron and magnesium alloys were all employed (152, 156).

From the PTCA era, restenosis was seen only as a consequence of balloon injury. With the introduction of stents in their various forms, a further dimension had been added. Was it possible that one design was better than

another? Did stent material make a difference? These questions were especially important as numerous stent designs could be created within a coil, tubular mesh, or slotted tube framework. In particular, especially with slotted tube stents, further distinction could be made between open cell and closed cell types (the latter do not change form even when the stents are flexed) (157). There were also differences in strut pattern or thickness. These parameters can affect properties such as elastic recoil or rigidity of the stent (158, 159). With regards to materials, alloys such as stainless steel known to contain nickel can cause allergic reactions and so could be relevant if this led to excessive inflammation in susceptible patients. There were therefore early calls for thorough evaluation of emerging stent technologies (155).

1.9.1 Mechanism of action

1.9.2.1 Self expanding versus balloon expandable

Early commercially available versions were the Wallstent™ (initially Schneider, then Boston Scientific, USA), a self-expanding tubular mesh stent with a platinum core and cobalt based alloy layer and the Palmaz-Schatz™ (Johnson and Johnson, USA), a balloon expandable, slotted tube stent made from 316L stainless steel (160). The rationale for using self-expanding versus balloon expandable was that they had more gentle mechanics of stent expansion aimed at reducing plaque fracture, edge dissections and distal embolisation of plaque debris. The two were compared in an observational study (161). Fifty patients (25 in each group), had follow up angiography including IVUS at a mean of six and a half months. There were differences in clinical and procedural factors. In the Wallstent group, more patients had a

history of MI (24% vs. 12%), more right coronary artery lesions were treated (52% vs. 13%) and coronary dissection was the indication for stenting in more patients (32% vs. 8%). Based on QCA and IVUS data, there was greater neointimal proliferation in the Wallstent group possibly due to chronic radial pressure exerted on the vessel wall. However, this also meant that there was considerable late vessel expansion (approximately 25% in terms of cross-sectional area) in this group and therefore overall, late loss was similar between the two. This tendency had also been observed in nitinol based self-expanding coronary stents in animal studies where stent struts had migrated into the adventitia (162). Other limitations including the profile of the delivery sheath making it more difficult to cross severe lesions, mesh design making side branch access difficult, stent deformation (160) and concerns about high rates of thrombotic occlusion (163) were among the reasons that led to the decline in self-expanding stent use.

In conclusion, although self expanding stents were the first to be implanted in coronary arteries, they had significant limitations and this led to greater focus on balloon expandable stents and their design.

1.9.2 Stent design

1.9.2.1 Coil versus tube stents

This discussion relates to balloon expandable BMSs. The Gianturco-Roubin™ (Cook,USA) was the first coronary stent approved by the FDA in 1993 (160). It was superseded by the GR-II™ (Cook,USA) made from 316L stainless steel with a coil design and was composed of a flat wire coil attached to a single

longitudinal strut (160). The previously mentioned Palmaz-Schatz stent, a modification of a peripheral artery prototype, demonstrated proof of concept for use in coronary arteries in an animal study (164). It was one of the first BMSs with a slotted tube design made from 316L stainless steel (160) and was used in the defining randomised trials versus PTCA that showed superiority of BMS in terms of restenosis (19, 20). Consequently it became one of the first commercially successful stents (165). As has already been highlighted, the differences between these stent designs can have an impact on properties such as elastic recoil and rigidity. Struts are generally wider apart in coil stents with fewer connections between them. Tubular stents were found to have less recoil compared to coil stents (158, 166). Coil stents were more flexible (159).

In a 'coil versus slotted tube' randomised, multicentre study of 755 patients between the GR-II and Palmaz-Schatz stents, there were better outcomes for the slotted tube design of the Palmaz-Schatz stents (nine month follow-up angiographic binary restenosis rates at of 47.3% for GR-II vs. 20.6% for Palmaz-Schatz, $p<0.001$) (167). This was attributed to greater stent recoil with the GR-II (acute gain 1.57±0.52mm vs. 1.76±0.54mm for Palmaz-Schatz, $p<0.001$) and increased tissue prolapse because of more open spaces between struts. A design independent difference had been that operators had undersized the GR-II stents by approximately 20% compared to the Palmaz-Schatz stents.

In another such randomised study the coil design Crossflex™ (Cordis, USA) stent and slotted tube NIR™ (Boston Scientific, USA) were compared in 223 patients (168). There was a significant difference in the six month

angiographic primary endpoint: MLD in the Crossflex group (1.94 +/- 0.79 mm) was less than in the NIR group (2.37 +/- 0.84 mm; P < 0.001). In contrast to the previous study, acute gain had been similar between the two groups. Consequently, late loss was also therefore higher in the Crossflex group. The binary restenosis rates were 26% and 17% in the Crossflex and the NIR groups, respectively (P = NS).

1.9.2.2 Open versus closed cell slotted tube stents

There was a signal that the coil design was less favourable than the slotted tube design and so the next generation of stents were predominantly based on the latter. But there was a need to incorporate some of the desirable properties from the coil design. Wider spaces between struts allowed more flexibility and also good side branch access. More contemporary BMS designs could therefore be further subdivided into 'open cell' and 'closed cell' tubular stents (Figure 7). The difference here was that closed cell stent designs do not change form even when flexed while open cell stents change conformation especially when cells grow (157). This would translate, in theory, to open cell designs having less radial strength (the external pressure that a stent is able to withstand without buckling or collapsing) and increased propensity to plaque prolapse but would be more conformable and have better side branch access compared to closed cell designs.

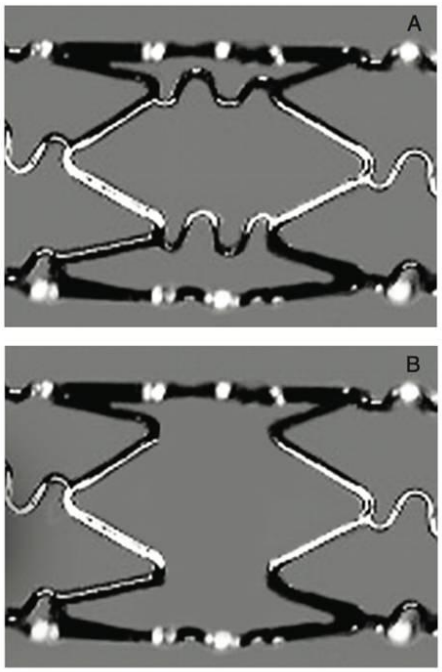


Figure 7. A) Closed cell versus B) Open cell design. Reproduced with permission from Cook JR, Haery C, Montoya A. M *J Invasive Cardiol 2011;23:E183–E187*

Feasibility of this concept was demonstrated with one of the first of these newer generation stents, the ACS Multi-Link™ (Guidant Corporation, now Abbott Vascular, USA) stent (169). This was a slotted tube stent made from 316L stainless steel with a pattern of repeating, non-overlapping loops connected by interposed bridges. In the Advanced Cardiovascular Systems MULTI-LINK Stent Clinical Equivalence in de Novo lesions Trial (ASCENT) trial, clinical and angiographic outcomes associated with this new stent design were compared to the Palmaz-Schatz stent in a randomised equivalency (or non-inferiority) trial design (170). At this time, the Palmaz-Schatz stent was the “gold standard” for regulatory-based stent comparisons. There were 1040 patients included in the study. Angiographic inclusion criteria were single,

focal, de novo lesions up to 20 millimetres in length, in vessels with an estimated reference diameter greater than three millimetres. The primary outcome of TVF (death, MI or TLR) within nine months of follow up was similar between the groups (15.7% for Multilink vs. 16.7% for Palmaz-Schatz, p = 0.42). A subset of patients was chosen for routine angiographic follow up and this occurred in 73% of the 521 patients eligible. Binary angiographic restenosis was 16.0% with Multilink compared to 22.1% for the Palmaz-Schatz group (p = 0.31). Although not a pre-specified endpoint, an interesting observation was that the Multilink had better deliverability with 30% fewer delivery failures but in addition to differences in stent design, there were also differences in the delivery sheath system between the stents.

Other studies, in contrast, have shown that differences in slotted tube stent design can result in different outcomes. In a randomised study of 1147 patients, patients received one of five different slotted tube stents all made from stainless steel: In Flow™(In Flow Dynamics, Germany), Multilink, NIR, Palmaz-Schatz and Pura-A (Devon Medical, Germany) (171). There was a statistically significant difference in the primary composite endpoint of death, MI and TLR at 1 year (ranging from 17.6% for the Multilink to 30.6% for the NIR, p = 0.004). Late loss ranged from 1.01 ± 0.70mm in the Multilink to 1.20 ± 0.84mm in the NIR (p = 0.09). After multivariate regression analysis, stent design remained a significant predictor of event free survival. In another study, the Multilink platform showed less tissue response when measured by IVUS compared with Palmaz-Schatz and In Flow stents (172). Mean intimal hyperplasia thickness (mm) was 0·16 ± 0·08, 0·26 ± 0·19, 0·39 ± 0·14 (p < 0·001) for the Multilink, Palmaz-Schatz and In Flow respectively.

1.9.2.3 Modular versus slotted tube stents

Another distinction that can be made between tubular stents is whether they are modular or the previously discussed slotted tube design. The modular cells are composed of rings welded together. This distinction has become less clear because of the open cell design of slotted tube stents which make them more like modular stents (153). The Microstent II™ (Arterial Vascular Engineering, USA), a type of modular stent made from stainless steel in a helical pattern laser fused from sinusoidal elements, was compared to the Palmaz-Schatz in the randomised SMART (The Microstent's ability to limit restenosis trial) trial (n=661). There was no difference in the primary endpoint of TLR (8.9% for Microstent II vs. 9.2% for Palmaz-Schatz, p = 0.83). Binary restenosis rates were also similar (25.2% for Microstent II vs. 22.1% for Palmaz-Schatz, p = 0.64).

1.9.2.4 Strut Thickness

Another important factor is the thickness of the stent struts. Thicker struts offer the theoretical advantage of better radial support but they may cause more injury to the vessel wall by stretching. On the other hand, whilst thinner struts may cause less angulation and stretching, they may slice into tissue more easily and therefore result in deeper injury.

In the Intracoronary Stenting and Angiographic Results Strut Thickness Effect on Restenosis Outcome (ISAR- STEREO) trial, Multilink stents with different strut sizes were compared (173). The original thinner strut size Multilink (50 μm) was compared to the newer but thicker strut Multilink Duet (140 μm). They were both made from stainless steel and were otherwise similar in

design apart from slightly more articulations between the struts in the thinner strut stent. There was significantly less late lumen loss with the thinner strut stent compared to the thicker strut size (0.94±0.74 versus 1.17±0.78 mm, p = 0.001). Also, the primary end point of the trial, one year angiographic restenosis, was reached in 15.0% of the thin-strut stent patients and 25.8% of the thick-strut stent patients (*p*=0.003). Of note in the thin strut group, stented segment length was longer and final diameter stenosis post stenting was lower. Both of these parameters would be expected to have a negative impact on restenosis. Multivariate analysis confirmed this. Both of these factors were independent predictors of increased risk of restenosis. In addition, after adjusting for these variables the risk of restenosis was still significantly lower in the thin strut group. The investigators subsequently showed that this difference occurred in the most complex lesions only (174). In ACC/AHA type B2 or type C lesions there was a significant reduction in restenosis in the thin-strut stent group (restenosis rate: 14.5% vs. 29.0%; P <.01 for thin-strut vs. thick-strut stents). The restenosis rate did not differ between stent designs in patients with noncomplex lesions (ACC/AHA type A or B1; restenosis rate: 16.7% vs. 16.7%, P = 1.0 for thin-strut vs. thick-strut stents).

In the ISAR-STEREO 2 trial, the thin strut 50 µm Multilink stent was compared to the BX Velocity stent (Cordis, USA), strut thickness 140 µm (64). The rationale for this study was to assess whether strut size made a difference in terms of restenosis in stents with different designs. The BX Velocity stent was a stainless steel, slotted tube stent with a closed cell design. Procedural data were also similar on this occasion and as with the previous study there was less restenosis in the thin strut group (17.9% vs. 31.4%, p < 0.001).

In another study with an observational design, stents from the Multilink platform were once again pitted against each other (175). The original Multilink with a strut thickness of 50 µm was compared with the next generation Multilink Duet (140 µm), Tristar (140 µm), Tetra (mean 96 µm, variable strut thickness system), Penta (mean 96 µm, variable strut thickness system), Ultra (100 µm), and Pixel (90 µm) stents and were used when they became available (see section 1.10). Stents with a strut thickness of greater than or equal to 90 µm were considered thick-strut stents (thin strut n = 287, thick strut n = 376). There were significant differences in clinical and procedural characteristics. Patients treated with a thick-strut stent less often had a history of myocardial infarction or PTCA, and were receiving statin therapy more often at the time of inclusion, representing a change in clinical practice over time. The thin stent group included more patients with a restenotic lesion and chronic total occlusion. Stent length and reference diameter before the procedure were higher in the thin strut group and lesion length was shorter in the thin strut group. At six to ten months follow up, binary angiographic restenosis was 17% in both groups ($p = 0.85$). Late loss was lower in the thin strut group (0.92 ± 0.59 vs. 1.06 ± 0.71, $p = 0.011$). After multivariate logistic regression with other factors identified from univariate analysis (history of PTCA, current smoking, reference diameter, stent length, restenotic lesions, and unstable angina pectoris) strut thickness showed an independent contribution to late loss.

In all of the strut thickness comparison studies mentioned above, there were no differences between the groups in terms of the clinical end points of death and myocardial infarction.

With regards to the evidence presented in this discussion, a number of conclusions can be drawn. Of the balloon expandable stents, the tubular designs performed better as compared to the coil design with regards to restenosis, but there was little or no difference between the different types of slotted tube designs. Based on superior procedure success results, open designs such as the open cell slotted tubes or modular stents were probably better with regards to deliverability. One caveat that should be mentioned is that the results of these studies are not necessarily applicable in all lesions. Many of the studies did not include complex lesions such as tortuous, calcified or excessively long lesions. This was noted in the strut thickness studies where the benefits of the thinner strut stents were seen in the more complex lesions. The strut thickness studies, in particular the ISAR-STEREO series of trials, showed that within the stainless steel stents employed in those trials, there was a clear pattern of less restenosis with thinner strut stents. These findings had a profound impact on evolving stents as the message from this to industry was that ‘thinner is better’. There was therefore a drive towards the use of higher radial strength materials that would allow reductions in stent strut thickness such as cobalt alloys.

1.9.3 Stent material

Materials tested and employed for manufacturing metallic stents were 316L stainless steel, platinum–iridium alloy, tantalum, nitinol, cobalt–chromium alloy, titanium and the biodegradable pure iron and magnesium alloys (Table 6) (156, 157). Of these, most of the early stents and indeed most of the evidence for intracoronary stent use were based on 316L stainless steel

stents (section 1.9.2). Regulatory approval for these stents led to the majority of commercially available stents being composed of 316L stainless steel. With the development of newer stents, there was a shift towards employing cobalt-chromium alloys although it is worth noting that one of the first stents, the Wallstent (section 1.9.1), used cobalt chromium alloys. This shift was mainly because the superior radial strength of cobalt chromium would allow production of lower profile, thin strut stents. They were also more visible fluoroscopically.

Material	Corrosion resistance	Radial strength	MRI compatibilty	Radiopacity	Bio-compatibility	Commercially available stents (2005)
316L SS	++	+	±	+	+	++
Pt–Ir	++	-	++	++	++	-
Ta	++	-	++	++	+	+
Ni–Ti	+	+	++	±	+	+
Co–Cr	++	++	++	++	++	+
Ti	++	-	++	±	++	-
Fe	++	+	+	+	++	-
Mg alloys	+	-	++	-	+	-

Table 6. Properties and of materials used in intracoronary stent and commercial availability. 316L SS = stainless steel, Pt–Ir = platinum–iridium alloy, Ta = tantalum, Ni–Ti = nitinol, Co–Cr = cobalt–chromium alloy, Ti = titanium, Fe = pure iron, Mg = magnesium alloys

The mechanical properties of the metals were also particularly important in stent development. The preferable mechanical properties include good elastic modulus, useful for preventing elastic recoil; high yield strength, the point at which the metal deforms permanently; and high tensile strength, the maximum stress that a material can withstand while being stretched or pulled before failing or breaking. For example, the relatively low tensile strengths of tantalum, pure iron and magnesium alloys theoretically make them more likely to fracture. Cobalt chromium and 316L stainless steel alloys appear to have the right balance of these mechanical properties with cobalt chromium having somewhat better parameters (Table 7) (156).

Metal	Elastic modulus(GPa)	Yield strength (MPa)	Tensile strength (MPa)
316L stainless steel	190	331	586
Cobalt chromium	210	448-648	951-1220
Tantalum	185	138	207
Titanium	110	485	760
Nitinol	83	195-690* 70-140†	895
Pure iron	211	120-150	180-210
Magnesium alloy	44	162	250

Table 7. Mechanical properties of metals used for making stents

*Austenite phase, † Martensite phase

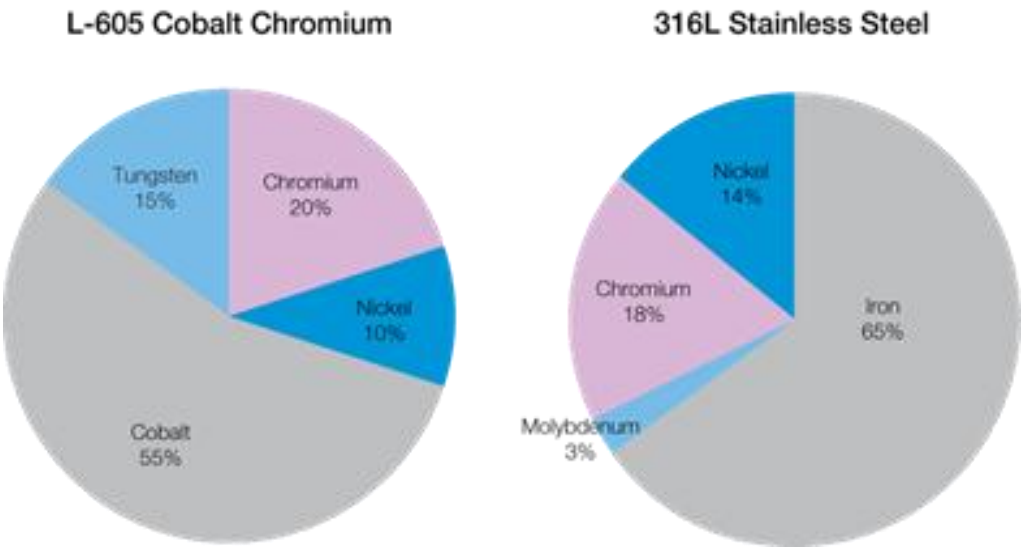


Figure 8. Chemical requirements for cobalt-chromium based on American Society for Testing and Materials, F90-97.Chemical requirements for 316L stainless steel based on American Society for Testing and Materials, F139-86.

Biocompatibility is another important issue. The weight percentage of nickel is slightly higher in 316L stainless steel (Figure 8) (156, 176). Allergic reactions to the release of nickel ions can occur among stainless steel implants. In particular, the release of nickel ions from 316L stainless steel stents may trigger local immune responses and inflammatory reactions, which in turn may induce intimal hyperplasia and in-stent restenosis (177). Metal ion release is not necessarily only related to the elemental proportions in an alloy but can be more influenced by stability and regeneration potential of the surface oxide formed when interacting with electrolytes. Nickel is disproportionately released from stainless steel whereas cobalt–chromium reforms the surface oxide faster than stainless steel leading to less nickel ion release (178). These may be important factors when considering the

disruption experienced by oxide films during stent deployment and therefore the likelihood of ion release from the respective materials. Attempts to try and circumvent this limitation by coating stainless steel stents (In Flow and NIR) with more biocompatible materials have been attempted including the use of gold coated stents but this resulted in a higher restenosis rate amongst the group treated with these types of stents (179, 180).

Stent coatings have also been used as a means of preventing both thrombogenicity and restenosis. Surface characteristics of a stent material can influence thrombosis and neointimal hyperplasia by affecting how the cells involved in thrombosis and neointimal hyperplasia adhere and proliferate (156). In addition to gold, a variety of inorganic coatings have been trialled including carbon (181), silicon carbide (182), iridium oxide (183) and titanium-nitride-oxide (184). Of these, only the titanium-nitride-oxide coated stents were shown to have less restenosis when compared with non-coated stents. Other types of coatings included the use of pharmacological agents such as heparin and components of cell membranes such as phosphorylcholine. However, randomised trials failed to show a benefit in terms of both restenosis and stent thrombosis in heparin-coated versus non-coated stents (185, 186) and phosphorylcholine coated stents also did not confer any benefit over non-coated stents (187). Although the reasons why each of these coatings was chosen have not been explored in detail, they were selected because, in most cases, encouraging preclinical work had suggested they would reduce the rates of BMS

stent thrombosis or restenosis (156, 157). In practice, however, the results have mostly been disappointing. However, the advent of DES, also a form of ‘coated stent’, has led to renewed interest in this field including more biocompatible polymers for drug elution (188).

The role of stent materials and coatings in preventing restenosis has been widely investigated. Early comparisons of stents were between stents made of the same material (primarily 316L stainless steel) and were primarily focused on stent design. The ‘game changer’ was the finding that thinner stent struts were associated with less restenosis compared to thicker strut stents. Despite no randomised trial data with regards the change in material, this led to a newer generation of stents made from cobalt-chromium alloys. Their superior radial strength and higher density allowed the production of thinner stent struts whilst maintaining deliverability and visibility. Stent coatings were an example of how early encouraging concepts may not translate into clinical benefit. Although this is a complex multi-factorial field, there was a need for a randomised trial to compare stainless steel stents with cobalt chromium stents. Whilst this cannot be taken as definitive evidence of alloy versus alloy because of differences in strut thickness and design, if one showed better restenosis characteristics than the other, it would give some strength to the arguments. If no difference, it may be that the expected reduction of restenosis due to reduced strut thickness with cobalt-chromium might be countered by some other factor. Ideally this comparison would be between stents of similar design. The Multilink platform offered the potential for this.

1.10 Multilink Zeta (316L stainless steel) vs. Multilink Vision (cobalt chromium) stents

In 2003, the seventh generation Multilink Vision™ (Guidant, now Abbott Vascular, USA) was one of the earliest cobalt chromium stents to get FDA approval (189). The Multilink stent system had evolved from 316L stainless steel stents beginning with the original ACS Multilink through to the sixth generation Multilink Zeta™. The original Multilink had a strut thickness of 50 μm compared with the next generation Multilink Duet (140 μm), Tristar (140 μm), Tetra (90-125 μm, variable strut thickness system), Penta (90-125 μm, variable strut thickness system). The original ACS Multilink was designed in the 'pre ISAR-STEREO era' and so the impact of thinner struts in practice had not yet been realised. Because of its low visibility thicker strut designs were favoured with newer generations. There were also other subtle redesigns in terms of links between cells as the series progressed in keeping with studies of that time (section 1.9.2). For example, compared with the Multilink Tetra stent, the Multilink Penta stent had a modified link pattern, which improved flexibility and scaffolding and allowed better expansion of cells to help maintain side-branch access when treating bifurcation lesions(Figure 9).

Figure 9. Evolution of the MULTI-LINK ™ stent system. Reproduced with permission from Abbott Vascular company documents.

The manufacturer's product information describes the Multilink Zeta as being identical to the Penta (190). They were slotted tube stents with an open cell design. The variable strut thickness was an innovative way to improve visibility whilst maintaining flexibility by using thinner curved struts and thicker straight struts for better visibility (Figure 10).

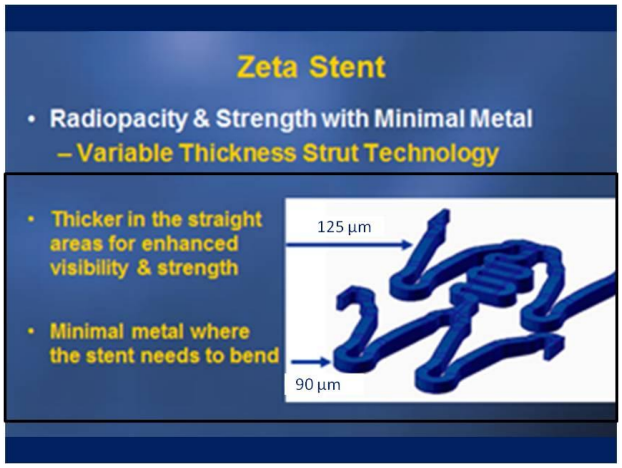


Figure 10. Variable thickness strut technology of the Multilink Zeta. Reproduced with permission from Abbott Vascular company documents.

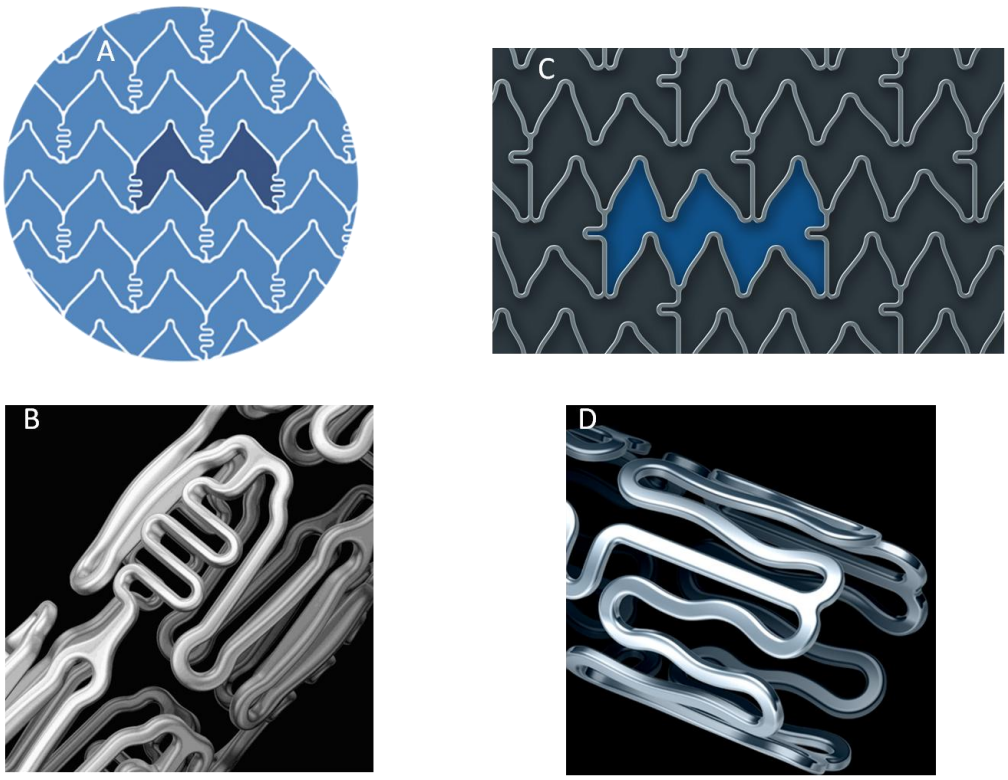


Figure 11. Design of the Multilink Zeta and Vision. A) Footprint of the Zeta stent. B) Close up of Zeta stent. C) Footprint of the Vision stent. D) Close up of the Vision stent. They are both open cell stents with only subtle differences in the articulations between the struts. Reproduced with permission from Abbott Vascular company documents.

The Multilink Vision is a chromium cobalt, balloon expandable, open cell slotted tube stent and is 81 μm thick (176) and has a similar design to the stainless steel Zeta stent (Figure 11). FDA approval was largely based on a prospective, multicenter registry (n=268) that demonstrated the efficacy of the Multilink Vision stent (176). In this study 23% of the patients were diabetic, 40% had complex lesions (ACC/AHA type B2 (33%) / C (7%), mean reference diameter was 2.94 mm and mean lesion length was 10.6 mm. The average stent length deployed per patient was 17.2 mm. The primary endpoint of target vessel failure

defined as a composite occurrence of death, myocardial infarction, and target vessel or target site revascularization was 6.7% at 180 days. Six month QCA parameters included mean reference diameter of 2.92 mm, late loss of 0.83 mm and a binary restenosis rate of 15.7%. The authors of this registry went on to compare late loss between the cobalt-chromium stent with historical data from earlier registries with other 316L stainless steel Multilink stents (191) without any statistical analysis. In these registries (n=575 with angiographic follow up), the number of diabetics (21%) were similar but more complex lesions were treated (AHA/ACC Type B2, 54-56%; Type C 6-10%). Mean reference diameter (3.0mm), lesion length (11.65 mm) and stent length (18.8 mm) were comparable. They showed that mean late loss was 0.83 mm in the 81µm Multilink Vision compared to mean late loss of 0.78 mm in the original ACS Multilink, 1.0 mm in the Duet and 1.05 mm in the Tetra. In comparison, the average binary restenosis rate for all the stents in the stainless steel registry was 19.6% (191).

The data for the Multilink Vision therefore appeared favourable. However, more firm conclusions could be drawn by performing a randomised comparison with a similar contemporary stainless steel design, the Multilink Zeta.

CHAPTER 2

Methodology

2.1Trial design

The SSTARS trial was a multicentre randomised controlled trial with a factorial design. Double randomisation occurred, prednisolone compared to placebo and cobalt chromium stent compared to stainless steel stent. This design allowed for evaluation of the two interventions simultaneously. In total, there were four possible treatment combinations, prednisolone and stainless steel stents, placebo and stainless steel stents, prednisolone and cobalt chromium stents and placebo and cobalt chromium stents.

2.2 Setting and Structure

The study was performed in the cardiothoracic units of The James Cook University Hospital, Middlesbrough, and the Royal Edinburgh Infirmary between January 2006 and October 2012.

The trial structure and committees were as follows:

Investigators

Dr. Andrew Turley - Chief Investigator, Consultant Cardiologist, The James Cook University Hospital, Middlesbrough

Dr. Zulfiquar Adam - Principal Investigator, Specialty training registrar and Research fellow, The James Cook University Hospital, Middlesbrough

Dr. Steven Jones - Co-investigator, Senior lecture/Consultant Endocrinologist, The James Cook University Hospital, Middlesbrough

Professor Rudy Bilous- Co-investigator, Senior lecture/Consultant Endocrinologist, The James Cook University Hospital, Middlesbrough

Independent data and safety monitoring committee

Dr V Connolly - Senior lecture/Consultant Endocrinologist, The James Cook University Hospital, Middlesbrough

Dr S Nag - Consultant Endocrinologist, The James Cook University Hospital, Middlesbrough

Dr R Bellamy - Senior Lecturer/Consultant Physician Infectious Diseases, The James Cook University Hospital, Middlesbrough

Clinical events committee

Dr Richard Graham -Consultant Cardiologist, The James Cook University Hospital, Middlesbrough

Sr Jackie Tough - Cardiology Nurse Consultant, The James Cook University Hospital, Middlesbrough

Steering committee

Dr. Mark de Belder -Consultant Cardiologist, The James Cook University Hospital, Middlesbrough

Dr Andrew Sutton - Consultant Cardiologist, The James Cook University Hospital, Middlesbrough

Dr. Neil Swanson - Consultant Cardiologist, The James Cook University Hospital, Middlesbrough

2.3 Study population and recruitment

Patients admitted for percutaneous coronary intervention for obstructive coronary artery disease were considered for the study. They were identified from the elective waiting list or were awaiting angiography after an acute coronary syndrome, whether presenting locally or from the inter-hospital transfer list.

For acute transfer patients, they were seen on the day of their transfer. Local patients were approached once a decision to perform angiography had been made. For elective patients, they were seen in a pre-admission clinic within 7-days of their planned procedure.

2.3.1 Inclusion criteria

Patients were included if they met the following criteria:

- Any patient awaiting percutaneous coronary intervention for symptomatic coronary artery disease (elective or acute).
- Documented myocardial ischaemia.
- Coronary angiography demonstrating at least a 50% reduction of the luminal diameter in at least one native coronary artery (as measured by quantitative computerised angiography).
- Any lesion for which the operator (interventional consultant cardiologist) felt a non-drug eluting stent was appropriate.

2.3.2 Exclusion criteria

Patients were excluded if they met any of the following criteria:

- Proposed use of a drug eluting stent (in the study lesion(s)).
- Left main stem stenosis
- Primary PCI for ST elevation myocardial infarction
- Steroid therapy within 30-days of study enrolment.
- Contraindication to corticosteroid use.
- Previous inclusion in this study.
- Non-cardiac disease likely to cause death within 6-months.
- Inter-hospital transfers from Cumbria (out of region).

2.3.2 General assessment

Following written informed consent, all patients had cardiovascular risk factors, past cardiac history, drug history, body mass index (BMI) and blood pressure recorded. Stable angina symptoms were defined according to the Canadian Cardiovascular Society (CCS) classification. The New York Heart Association (NYHA) classification was used to classify breathlessness.

2.3.3 Medical management

The administration of pharmacological agents including aspirin, clopidogrel, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, statins, nitrates and calcium channel blockers was at the discretion of the attending physician. Clopidogrel 75mg daily (for four days pre-PCI) or if less than four days pre-PCI two loading doses of 300mg followed by 75mg daily was commenced.

2.4 Randomisation

The trial featured a mixed single and double blinded randomised controlled design where both the patients and the physicians performing PCI were blind to the prednisolone/placebo allocation but only the patients were blinded to the stent allocation. Patients were block randomised to prednisolone or placebo prior to angiography and subsequently to cobalt chromium or stainless steel stent once eligibility was confirmed angiographically.

2.4.5 Steroid randomisation procedure

For the first randomisation, participants were randomly allocated in a 1:1 ratio to receive prednisolone or matched placebo according to a randomisation sequence generated in advance by software called Prisym 2000. The tablets were manufactured and provided by Sharp Clinical Services (Powys, Wales, UK). The first randomisation was produced in 2005 and was generated for 500 patients as a balanced block of four and subsequently further consignments for 250 patients at a time were produced as the trial progressed. Individual sealed envelopes containing treatment allocations were given to trial pharmacists in both centres. Treatment allocation was masked from all trial personnel and participants.

Elective patients were randomised at the time of their pre-admission clinic attendance (one week prior to the procedure) and assigned to the respective study arms.

Urgent patients were randomised before their procedure and assigned to the respective study arms.

2.4.6 Stent randomisation procedure

For the second randomisation between stainless steel and cobalt chromium stents, participants were also randomised in a 1:1 ratio in blocks of 10 using the open source statistical programme R by a hospital audit officer who was not part of the trial team. R is a free software environment for statistical computing and graphics. It compiles and runs on a wide variety of UNIX platforms, Windows and Mac OS and is available for free download from http://www.r-project.org. To use the package commands are typed in to the R console window, the command used to generate binomial random variables is the rbinom function (192). The command takes the following arguments rbinom (n, size, probability) (Figure 12). Again, individual sealed envelopes were used and given to the research nurses once the participant's coronary anatomy was deemed suitable for the trial.

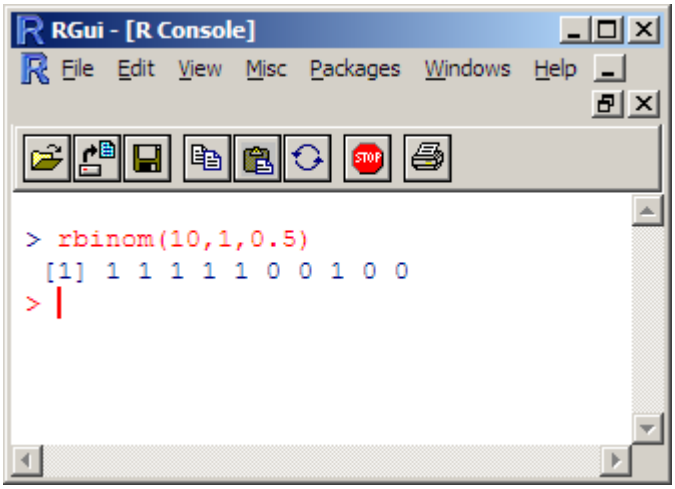


Figure 12. An example of the generation of 10 random variables between 0 and 1. The numbers 0 and 1 were used to randomly assign the letters A and B for the second randomisation arm in the SSTARS study.

2.5 Registry

Patients found to be ineligible were withdrawn from the main study and instead entered into a registry. The trial initially recruited mainly elective patients in whom angiographic status was known prior to recruitment but over the course of the trial most patients progressively underwent PCI immediately following angiography. This was mainly because there was a shift towards performing more urgent coronary angiography for ACS patients.

2.6 Medication and procedures

2.6.1 Medication protocol

Patients were randomised to oral prednisolone or placebo. The first dose had to be administered at least six hours pre-procedure and this was to continue for a total of 28-days. The dosing regimen for prednisolone is shown (Table 8).

Days	Dose
1-14	40mg
15-19	20mg
20-24	10mg
25-28	5mg

Table 8. Prednisolone dosing regimen.

Study drug was handled in accordance with the protocol and the container label. The study medication was stored in a locked, designated, study drug cabinet. Study drug was dispensed by a suitably qualified and designated member of staff under the guidance of a hospital pharmacist.

Due to dual oral antiplatelet therapy plus oral corticosteroid use, all patients received empirical proton pump inhibitor cover (Lansoprazole 30mg/day for 28-days) for the duration of the glucocorticoid/placebo course.

2.6.2 Coronary angiography and PCI

Coronary angiography was performed in the standard manner (Judkin technique) via femoral or radial artery puncture. The angiographic information recorded was the extent of coronary artery disease (1 vessel disease (VD), 2 VD with proximal left anterior descending artery, 2 VD + other, 3 VD, 4 VD [i.e. including a large intermediate vessel as a fourth vessel], left main stem (LMS), normal coronaries or minor disease), modified “Duke” score and AHA/ACC lesion class. A 50% reduction in luminal diameter was classed as significant for left main stem lesions.

As described earlier, all patients were pre-treated with clopidogrel as per unit protocol. After sheath insertion, a bolus of heparin was administered (dose: weight related with a minimum of 70u/kg).

Lesion predilation was recommended using standard balloons and guidewires, with the operator choosing the balloon size and stent size. Inflation pressures, duration of inflations and stent length and diameter were recorded. Glycoprotein IIb/IIIa receptor blocker treatment was given at the discretion of the interventional cardiologist once the patient was in the coronary angiography lab.

Lesions in large vessels were treated according to randomisation between stainless steel Multi-link Zeta™ (Guidant/Abbott vascular, USA) and cobalt chromium Multi-Link Vision™ (Guidant/Abbott vascular, USA) stents. These stents were commercially available stents. Lesions in small vessels were treated with sirolimus-eluting

Cypher Select® stents (Cordis, USA). After the procedure, arterial sheath removal occurred once the activated clotting time (ACT) fell below 150 seconds in the case of femoral sheath insertion. For procedures performed via the radial artery, the sheath was removed immediately post procedure with the application of a TR band® (Terumo) for haemostasis as per standard practice in the unit.

Patients continued to receive aspirin 75mg od (at least) indefinitely and Clopidogrel 75mg once daily for a minimum of 4 weeks.

2.7 Quantitative coronary angiography

Quantitative angiography analysis was done by use of the automated edge-detection system (Philips Inturis) a research fellow. Thirty randomly selected measurements were reanalyzed by the same research fellow. Results were reproducible. The mean of the difference between measurements was 0.09 ± 0.3 mm ($p = 0.55$) for MLD and 0.10 ± 0.25 mm ($p = 0.31$) for diameter stenosis.

Measurements were made in diastole and performed in two orthogonal views after administration of 200µg of intracoronary nitrate. The contrast filled guiding or diagnostic catheter was used for magnification calibration. Quantitative coronary angiography measures included: minimal luminal diameter (MLD); reference diameter, derived as either an average of the proximal and distal reference diameters or the interpolated diameter derived by the software for the selected segment; percent diameter stenosis; in-stent restenosis, defined as ≥50% diameter stenosis within the stent at follow up; in-segment restenosis,

defined as ≥50% stenosis within the stented segment or within 5mm proximal or distal to the stent edges; acute gain, defined as the difference between MLD after stent implantation and the MLD before PCI; late loss, defined as the difference between the MLD after stent insertion and the MLD at follow up; net gain, defined as the difference between acute gain and late loss.

2.8 Follow up

Patients were seen by a research nurse at three intervals. They were seen seven days after taking the first dose of study medication, subsequently at 30 days and finally when they attended for their follow up angiogram at six months. For registry patients there was only telephonic follow up at six months.

2.8.1 Clinical assessment

Mortality, non-fatal ischaemic event rate (re-admission rates for an ACS), additional revascularisation rate, NYHA and CCS classification data, and repeat hospitalisation rates were collected at each follow up visit for all patients recruited into the study.

2.8.2 Blood tests

Blood samples were taken from all patients as part of the standard pre-assessment work-up for percutaneous coronary intervention (full blood count, coagulation, urea and electrolytes, serum glucose/HBA1c and lipid profile). These samples were fasting samples. Once the patient

was entered into the study, further samples were taken for the measurement of highly sensitive CRP (hs-CRP) at different intervals prior to and after PCI.

Serum hs-CRP was stored for subsequent analysis in a –80^{o}C freezer. The samples were measured in batches after the patient had undergone coronary revascularisation. Biochemistry scientists were blinded to the clinical condition and angiographic findings of the study cohort.

All patients also had fasting serum glucose and glycated haemoglobin (HbA1c) checked seven days post PCI, on completion of the oral prednisolone course and at the time of angiographic follow up.

Due to the potential problem of hyperglycaemia in patients randomised to corticosteroid treatment, all patients were given home monitoring BM sticks. Prior to hospital discharge they were instructed on the correct use of home monitoring by a qualified cardiology or research nurse. They were also educated on normal values and provided with contact details of the research team, in hours, or cardiology on call team, out of hours, for support and advice if their BM recordings were high.

2.8.3 Angiographic assessment

A follow up coronary angiogram was performed six months after the initial procedure or earlier if clinically indicated. The follow up angiogram was also performed using standard techniques and 200μg

of intracoronary nitrate was administered using the same projections as the baseline angiogram.

Follow up was terminated after an end-point had been attained or the follow up angiogram had been performed. The time window for performing diagnostic angiography was 6 ± 2months. A time window was included for the six month angiogram because it would not always be possible to perform an angiogram exactly at six months. There are various reasons for this including clinical priority overriding research interests during busy periods, patient preference for angiogram to be delayed due to personal circumstances or clinical need to delay angiography.

2.9 Outcome measures

The primary endpoint was in-stent restenosis determined angiographically as restenosis of at least 50% diameter within the stent segment at 6 months follow-up, or determined earlier for clinical reasons.

Angiographic measures included minimal luminal diameter (MLD) and reference diameter determined proximally, distally, averaged and interpolated; as well as derived measures percent diameter stenosis, late loss, acute gain and net gain. Anticipated major complications death, myocardial infarction, cerebrovascular accident and repeat hospitalisation were recorded together with revascularisation, ECG and cardiac markers changes.

2.10 Withdrawal and safety

Patients could withdraw from the trial at any point without alteration in standard care. The patient could be withdrawn if their attending clinician judged that circumstances arose as a consequence of being in the trial that were detrimental to the individual. All patients were monitored for bleeding or hyperglycaemia due to steroid administration. Adverse events were recorded according to expectedness and relatedness.

2.11 Ethics and governance

Conduct of the trial was subject to local site and London Multicentre Research Ethics Committee (MREC) approvals (ref: 04/MREC2/061) and registered with UK Trials (ISRCTN 05886349).

CHAPTER 3

Statistical Analysis

The primary research question was whether treatment with steroids was associated with a reduction in the proportion of patients experiencing in-segment restenosis. The study also investigated whether any such benefit was available with both stainless steel and cobalt chromium stents. The in-segment restenosis rate of the cobalt alloy stent was estimated to be 15% based on registry data available at the time (176, 193), compared to 30% for the stainless steel. This effect size between stents was likely to be smaller than the difference for the estimated effect of prednisolone. The IMPRESS study using prednisolone and stainless steel stents demonstrated a reduction in the in-segment re-stenosis rate from 33% to 7% (125).

Participants were randomised in a balanced 2 x 2 factorial design. Using the smaller effect size of 15% (for the stent comparison), and assuming loss to follow-up of 15%, a value for α of 0.05 and a power (1-β) of 80%, 137 patients per group (548 in total) would be needed, provided there was no interaction between the two comparisons. The sample size would thus be sufficiently large to detect both the effect of administration of prednisolone and of cobalt chromium stents assuming no interaction.

In factorial designs, if interaction is an important factor a Variance Inflation Factor (VIP) is needed to ensure sufficient power to detect the two effects and their interaction (only a factorial design is capable of investigating interactions). The maximum theoretical inflation requires a

doubling of the sample sizes for each effect (making the sample 4 times larger overall) (194).

In this case, the sample size would be approximately two fifths larger than needed (in the absence of interaction) to detect the predicted effect size for the use of steroid because the sample size had been calculated using the smaller effect size for the difference between stents (i.e. 15% rather than 26%). This conservative sample size calculation therefore allowed some room for interaction whilst achieving a statistically significant result for use of steroids. If an important interaction did exist, the benefit of one of the stents may not achieve statistical significance and further research would be needed to investigate this unexpected phenomena. The loss to follow-up estimate was also conservative at 15%.

As outlined in Chapter 4, the planned sample size was not achieved and 315 patients were recruited within the constraints of unplanned complexities for patient identification and recruitment. The power calculation for the study was revisited prospectively before analysis of trial data and informed by recent evidence. Assuming restenosis occurred in 30% of patients, and that both cobalt chromium stenting and prednisolone might halve the risk of restenosis, the average ‘intervention rate’ would be 11.25% and the average ‘control’ would be 22.5% within each comparison group. Assuming alpha=5%, the trial now had 72% power to detect an absolute difference of 11.25% between groups, assuming a two-sided test (nQuery+nTerim 2.0).

Analysis was performed by the principle of intention to treat (ITT), with analyses conducted according to assignment at randomisation (195, 196). Primary inference was based on the primary endpoint analysis as a difference in proportions, using Fisher's exact test (197) with statistical significance at the 5% level (2-sided), for combined stent groups and drug groups. Analyses of all secondary endpoints and adjusted analyses were considered supportive to the primary analysis so no adjustments for multiple comparisons were made.

Sensitivity analysis of the primary endpoint was analysed at the level of the patient and lesion using generalized linear models (GLMs) with separate indicator variables for steroid and stent groups as well as their interactions. Secondary analyses explored changes in angiographic measures using GLMs (198, 199), and the role of covariates such as CRP level . Major adverse cardiac events (MACE) such as death were analysed as time-to-event by survival analysis to compare hazard of death in the comparison groups.

Patient demographics and other study endpoints involving categorical variables were estimated using Fisher's exact test; continuous measures were evaluated using Students t-test where appropriate, otherwise suitable non-parametric tests were used.

Intention to treat principle allows for modification due to missing data, for which there is no completely satisfactory remedy since strong assumptions are required regardless of the approach taken(198, 200).

CHAPTER 4

Results

Between January 2006 and March 2012, 893 patients were recruited into the study having been randomised to either placebo or prednisolone (Figure 13). Of these, 315 patients underwent a second randomisation and were included in the main study. A total of 359 lesions were treated. The remaining 578 patients were entered into the registry (see section 4.7). The trial was terminated early because changes in clinical practice, with a rapid increase in the use of DES and an increase in the use of follow-on angioplasty for both elective and acute cases (where first randomisation occurred prior to the angiographic findings), made continuation increasingly difficult.

4.1 Baseline characteristics

The mean age of participants was 60 years (range 37 to 87 years), 85% were male, 42% were elective PCI cases and the mean number of lesions treated was 1.14 (range 1 to 4). As far as conventional risk factors for coronary artery disease were concerned, 11% were diabetic, 56% had a positive family of ischaemic heart disease, 51% had a history of hypertension, 89% had hypercholesterolaemia and 65% had a history of smoking.

Groups were similar at baseline, there were no significant or important baseline differences comparing groups apart from the maximum balloon inflation pressures between prednisolone and placebo (16.3 atm vs. 17.0 atm, p=0.02) (Tables 9-11). In particular, there was no statistically significant difference in the proportion of diabetics, AHA/ACC complex lesions (type B2 or C) or lesion length and stent

length which are all risk factors for restenosis. Of 315 patients, 308 (98%) received the treatment allocated to them. Failure to receive allocated therapy only occurred after the second randomisation where failed PCI with the study stent resulted in a non-study stent being used.

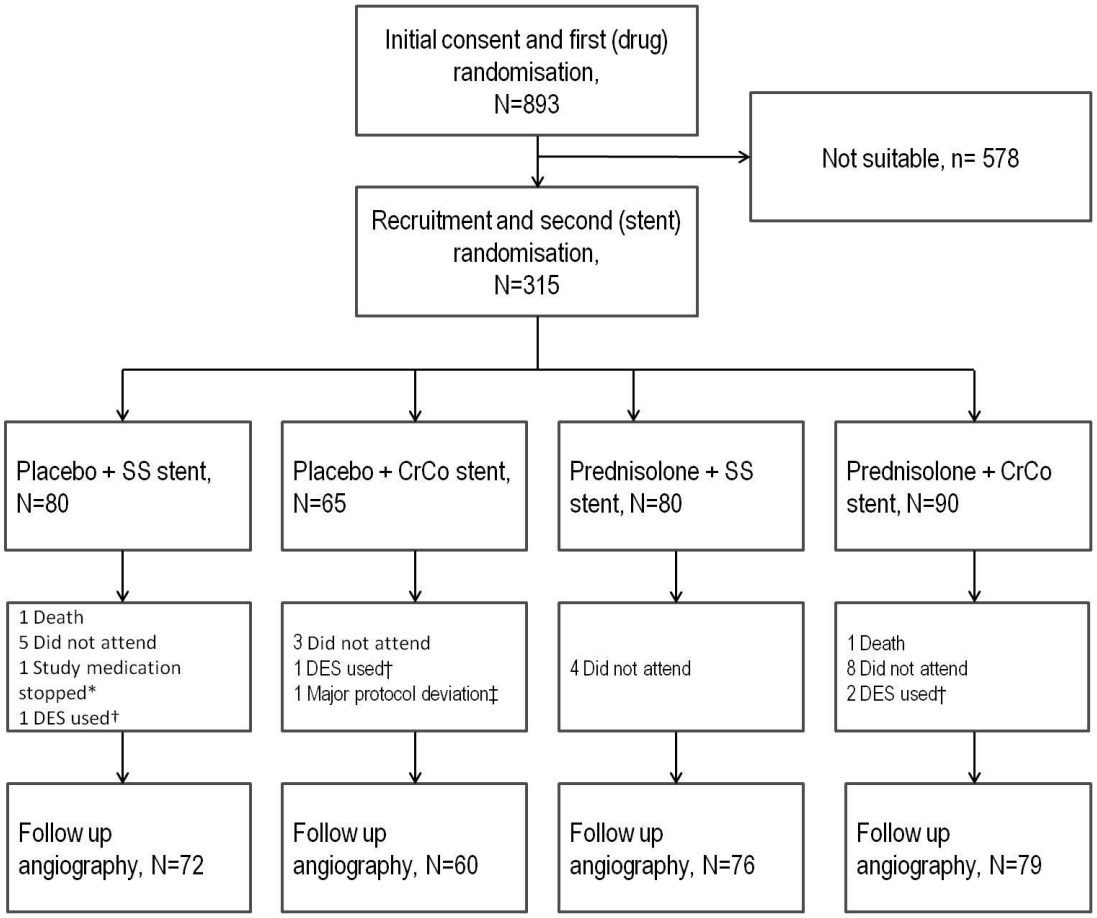


Figure 13. Consort diagram. *Physician directed, †Failure to deliver study stent, ‡ Saphenous vein graft treated (study exclusion criteria).

	Placebo				Prednisolone				Drug*			Stent*		
	CoCr	N=65	SS	N=80	CoCr	N=90	SS	N=80	Pl	Pred	p	CoCr	SS	p
Actual treatment	64	(98.5%)	79	(98.8%)	87	(96.7%)	78	(97.5%)	100%	100%	-	97%	98%	
Male	56	(86.2%)	68	(85.0%)	74	(82.2%)	71	(88.8%)	85.5%	85.3%	1.00	83.9%	86.9%	0.52
Age, y	60.2	(9.6)	60.0	(8.5)	59.5	(10.3)	62.2	(9.7)	60.1	60.8	0.54	59.8	61.1	0.23
Height, m	1.73	(0.08)	1.74	(0.09)	1.73	(0.09)	1.74	(0.08)	1.73	1.74	0.89	1.73	1.74	0.38
Weight, kg	85.5	(17.6)	87.5	(15.4)	88.9	(18.8)	86.7	(14.7)	86.6	87.9	0.50	87.5	87.1	0.82
Smoking status											0.67			0.53
never smoked	22	(33.8%)	30	(37.5%)	33	(36.7%)	24	(30.0%)	35.9%	33.5%		35.4%	33.8%	
ex-smoker	19	(29.2%)	30	(37.5%)	33	(36.7%)	33	(41.3%)	33.8%	38.8%		33.5%	39.4%	
current smoker	24	(36.9%)	20	(25.0%)	24	(26.7%)	23	(28.8%)	30.3%	27.6%		31.0%	26.9%	
History of hypertension	35	(53.8%)	42	(52.5%)	50	(55.6%)	35	(43.8%)	53.1%	50.0%	0.65	54.8%	48.1%	0.26
Family history of IHD	40	(61.5%)	42	(52.5%)	50	(55.6%)	45	(56.3%)	56.6%	55.9%	0.91	58.1%	54.4%	0.57
Previous MI	9	(13.8%)	10	(12.5%)	8	(8.9%)	12	(15.0%)	13.1%	11.8%	0.73	11.0%	13.8%	0.50
Previous CABG	3	(4.6%)	0	(0.0%)	1	(1.1%)	1	(1.3%)	2.1%	1.2%	0.67	2.6%	0.6%	0.21
Previous PCI	0	(0.0%)	3	(3.8%)	5	(5.6%)	7	(8.8%)	2.1%	7.1%	0.06	3.2%	6.2%	0.29
Previous TIA/CVA	1	(1.5%)	1	(1.3%)	3	(3.3%)	4	(5.0%)	1.4%	4.1%	0.19	2.6%	3.1%	1.00
History of PVD	1	(1.5%)	4	(5.0%)	4	(4.4%)	0	(0.0%)	3.4%	2.4%	0.74	3.2%	2.5%	0.75
History of LVSD	2	(3.1%)	7	(8.8%)	3	(3.3%)	5	(6.3%)	6.2%	4.7%	0.62	3.2%	7.5%	0.13
Renal disease	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0.0%	0.0%	-	0.0%	0.0%	-
Diabetes (I or II)	6	(9.2%)	8	(10.0%)	13	(14.4%)	7	(8.8%)	9.7%	11.8%	0.59	12.3%	9.4%	0.47
Insulin diabetic	1	(1.5%)	2	(2.5%)	2	(2.2%)	0	(0.0%)	2.1%	1.2%	0.67	1.9%	1.2%	0.68
Hypercholesterolaemia	61	(93.8%)	72	(90.0%)	76	(84.4%)	70	(87.5%)	91.7%	85.9%	0.11	88.4%	88.8%	1.00

Table 9. Baseline demographic data and risk factors. Count data shown as: count (%); comparisons: Fisher's exact test. Numeric data shown as: mean (SD); comparisons: independent samples t-test. *For drug comparisons and stent comparisons only % and mean.

CoCr = cobalt chromium, SS = stainless steel, Pl = placebo, Pred = prednisolone, IHD = ischaemic heart disease, MI = myocardial infarction, CABG = coronary artery bypass grafting, PCI = percutaneous coronary intervention, TIA = transient Ischaemic attack, CVA = cerebrovascular accident, PVD = peripheral vascular disease, LVSD = left ventricular systolic dysfunction

	Placebo				Prednisolone				Drug			Stent		
	CoCr	N=65	SS	N=80	CoCr	N=90	SS	N=80	Pl	Pred	p	CoCr	SS	p
Elective PCI	26	(40.0%)	35	(43.8%)	37	(41.1%)	34	(42.5%)	42.1%	41.8%	1.00	40.6%	43.1%	0.73
ACS type											0.58			0.81
unstable angina	11	(16.9%)	6	(7.5%)	14	(15.6%)	14	(17.5%)	11.7%	16.5%		16.1%	12.5%	
non-STEMI	25	(38.5%)	32	(40.0%)	34	(37.8%)	29	(36.3%)	39.3%	37.1%		38.1%	38.1%	
STEMI	3	(4.6%)	7	(8.8%)	5	(5.6%)	3	(3.8%)	6.9%	4.7%		5.2%	6.2%	
Cholesterol, mmol/L	4.9	(1.1)	4.6	(1.3)	4.8	(1.3)	4.5	(1.0)	4.73	4.63	0.46	4.82	4.54	0.04
Creatinine value, µmol/L	91.1	(17.4)	94.0	(18.8)	90.5	(20.3)	93.4	(15.5)	92.7	91.8	0.67	90.8	93.7	0.15
Troponin, µg/L	1.35	(4.65)	4.63	(11.54)	1.39	(2.75)	1.98	(5.52)	3.14	1.66	0.17	1.37	3.32	0.07
GPIIb/IIIa type											0.88			0.21
none	38	(58.5%)	47	(58.8%)	53	(58.9%)	44	(55.0%)	58.6%	57.1%		58.7%	56.9%	
Abciximab	26	(40.0%)	30	(37.5%)	37	(41.1%)	32	(40.0%)	38.6%	40.6%		40.6%	38.8%	
Tirofiban	1	(1.5%)	2	(2.5%)	0	(0.0%)	4	(5.0%)	2.1%	2.4%		0.6%	3.8%	
Number of lesions											0.46			0.72
1	59	(90.8%)	71	(88.8%)	77	(85.6%)	69	(86.3%)	89.7%	85.9%		87.7%	87.5%	
2	4	(6.2%)	9	(11.3%)	12	(13.3%)	10	(12.5%)	9.0%	12.9%		10.3%	11.9%	
3	1	(1.5%)	0	(0.0%)	1	(1.1%)	1	(1.3%)	0.7%	1.2%		1.3%	0.6%	
4	1	(1.5%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0.7%	0.0%		0.6%	0.0%	

Table 10. Baseline clinical and biochemistry characteristics. Count data shown as: count (%); comparisons: Fisher's exact test. Numeric data shown as: mean (SD); comparisons: independent samples t-test. *For drug comparisons and stent comparisons % and mean only.

CoCr = cobalt chromium, SS = stainless steel, Pl = placebo, Pred = prednisolone, ACS = acute coronary syndrome, STEMI = ST elevation myocardial infarction, GP IIb/IIIa= glycoprotein IIb/IIIa inhibitor

	Placebo				Prednisolone				Drug*			Stent*		
	CoCr	N=74	SS	N=89	CoCr	N=104	SS	N=92	Pl	Pred	p	CoCr	SS	p
Vessels treated											0.77			0.18
Protected LMS	0	(0.0%)	0	(0.0%)	1	(1.0%)	0	(0.0%)	0.0%	0.6%		0.6%	0.0%	
LAD	26	(35.1%)	39	(43.8%)	43	(41.3%)	45	(48.9%)	41.4%	43.5%		39.4%	45.6%	
Cx	14	(18.9%)	19	(21.3%)	19	(18.3%)	21	(22.8%)	20.7%	22.4%		20.0%	23.1%	
Int	1	(1.4%)	1	(1.1%)	2	(1.9%)	0	(0.0%)	1.4%	1.2%		1.9%	0.6%	
RCA	32	(43.2%)	30	(33.7%)	39	(37.5%)	26	(28.3%)	35.9%	32.4%		37.4%	30.6%	
SVG	1	(1.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0.7%	0.0%		0.6%	0.0%	
AHA/ACC lesion type											0.78			0.61
A	6	(8.1%)	8	(9.0%)	10	(9.6%)	7	(7.6%)	8.6%	8.7%		9.0%	8.3%	
B1	36	(48.6%)	41	(46.1%)	56	(53.8%)	45	(48.9%)	47.2%	51.5%		51.7%	47.5%	
B2	19	(25.7%)	25	(28.1%)	25	(24.0%)	19	(20.7%)	27.0%	22.4%		24.7%	24.3%	
C	13	(17.6%)	15	(16.9%)	13	(12.5%)	21	(22.8%)	17.2%	17.3%		14.6%	19.9%	
Max balloon pressure	16.9	(2.7)	17.0	(2.3)	16.3	(2.3)	16.3	(2.5)	17.0	16.3	0.02	16.5	16.7	0.62
No. of inflations	5.5	(4.3)	5.0	(3.3)	5.5	(3.6)	5.4	(2.9)	5.2	5.5	0.51	5.5	5.2	0.45
Total inflation time (s)	84.8	(69.0)	71.5	(52.2)	77.0	(52.9)	75.4	(42.4)	77.2	76.3	0.88	80.1	73.4	0.31
Lesion length, mm	13.8	(6.5)	13.4	(7.1)	13.9	(7.9)	14.6	(6.6)	13.6	14.2	0.41	13.9	14.0	0.86
Stent length, mm	19.2	(7.1)	20.2	(9.3)	20.7	(9.9)	21.2	(8.4)	19.7	20.9	0.20	20.1	20.7	0.54

Table 11. Baseline procedural data. Count data shown as: count (%); comparisons: Fisher's exact test. Numeric data shown as: mean (SD); comparisons: independent samples t-test. *For drug comparisons and stent comparisons % and mean only.
CoCr = cobalt chromium, SS = stainless steel, Pl = placebo, Pred = prednisolone, LMS = left main stem, LAD = left anterior descending, Cx = circumflex, Int = intermediate, RCA = right coronary artery, SVG = saphenous vein graft, ACC/AHA = American College of Cardiology/ American Heart Association.

4.2 Angiographic measures

Reference and minimal luminal diameters, with derived levels of stenosis are shown for all lesions in Table 12. In terms of risk factors for restenosis, the reference vessel diameters were not significantly different. There was also no evidence of difference in stenosis by any measure before or after PCI, or at follow up. Across all groups, average in-segment stenosis was: 70.3% (95%CI: 68.8% to 71.7%) at baseline prior to PCI; 6.6% (95%CI: 5.9% to 7.3%) immediately post-PCI; and, 35.2% (95%CI: 33.3% to 37.0%) at final follow up. Acute gain was 2.07mm (95%CI: 2.02 to 2.13mm), late loss was 1.04mm (95%CI: -0.98 to 1.10mm) and net gain was 1.04 (95%CI: -0.97 to 1.12mm).

From the angiographic data, a few observations can be made:

- The interpolated diameter was numerically less than the averaged particularly in the values pre-PCI. This may be because this measurement takes account of the tapering of the vessel from proximal to distal vessel. The interpolated diameter has the advantage of not requiring as much user interaction.
- At follow up, the reference vessel diameter was significantly less than after PCI (average reference diameter post PCI 3.24 ± 0.39 vs. 3.06 ± 0.40, $p<0.01$). This is also seen in other studies using similar stents (171, 175, 176) and may be a marker of neointima within the proximal and distal reference segments or negative remodelling.

- Overall, there were no significant differences between any of the parameters in either the drug or stent arms of the study. This is consistent before and after PCI and at follow up.
- The mean reference vessel diameters and lesion lengths were in line with the technology appraisal by the National Institute of Health and Care Excellence (NICE) recommending the use of drug eluting stents in arteries less than 3mm in diameter or lesions greater than 15mm in length (201). In other words, in line with the NICE recommendations, most lesions in this trial of bare metal stents were relatively short and in larger vessels, although patients with longer lesions and smaller reference diameters were included.

	Placebo n=163				Prednisolone n=196				Drug					Stent				
	SS	N=89	CoCr	N=74	SS	N=92	CoCr	N=104	Placebo	N=163	Pred	N=196		SS	N=181	CoCr	N=178	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	p	Mean	SD	Mean	SD	p
Pre-PCI reference diameters,																		
averaged	3.17	(0.45)	3.19	(0.41)	3.18	(0.40)	3.19	(0.44)	3.17	(0.43)	3.19	(0.42)	0.83	3.18	(0.43)	3.19	(0.42)	0.79
interpolated	3.06	(0.51)	3.02	(0.45)	3.09	(0.48)	3.08	(0.49)	3.04	(0.49)	3.08	(0.49)	0.42	3.07	(0.49)	3.06	(0.47)	0.73
Post-PCI reference diameters, mm																		
averaged	3.17	(0.41)	3.23	(0.38)	3.24	(0.35)	3.26	(0.43)	3.20	(0.40)	3.25	(0.39)	0.22	3.21	(0.38)	3.25	(0.41)	0.30
interpolated	3.15	(0.41)	3.16	(0.41)	3.19	(0.36)	3.20	(0.45)	3.15	(0.41)	3.20	(0.41)	0.33	3.17	(0.39)	3.18	0.43	0.77
6-month PCI segment computer-derived*																		
averaged	3.04	(0.42)	3.04	(0.40)	3.07	(0.36)	3.06	(0.42)	3.04	(0.41)	3.07	(0.39)	0.55	3.06	(0.39)	3.05	(0.41)	0.98
interpolated	2.96	(0.46)	2.96	(0.43)	2.99	(0.37)	3.00	(0.45)	2.96	(0.45)	2.99	(0.41)	0.49	2.97	(0.42)	2.98	(0.44)	0.90
Minimum luminal diameters, mm																		
Pre-PCI [A]	0.96	(0.40)	1.02	(0.48)	0.96	(0.40)	0.96	(0.46)	0.99	(0.44)	0.96	(0.44)	0.55	0.96	(0.41)	0.98	(0.47)	0.55
Post PCI, in-stent [B]	3.00	(0.39)	3.00	(0.33)	3.02	(0.35)	3.04	(0.40)	3.00	(0.37)	3.03	(0.38)	0.52	3.01	(0.37)	3.02	(0.37)	0.71
Follow up, in-stent [C]*	1.94	(0.62)	2.05	(0.48)	2.03	(0.59)	1.97	(0.56)	1.99	(0.56)	2.00	(0.58)	0.94	1.99	(0.60)	2.01	(0.52)	0.73
Pre-PCI stenosis, %																		
averaged	69.6%	(12.3%)	68.1%	(14.2%)	70.2%	(11.6%)	69.9%	(14.1%)	69.0%	(13.2%)	70.0%	(12.9%)	0.44	69.9%	(11.9%)	69.2%	(14.1%)	0.58
interpolated	68.6%	(12.8%)	67.0%	(14.8%)	69.4%	(11.8%)	68.9%	(14.7%)	67.9%	(13.7%)	69.1%	(13.3%)	0.38	69.0%	(12.2%)	68.1%	(14.7%)	0.50
Post-PCI stenosis, %																		
in-stent averaged	5.4%	(5.7%)	7.1%	(6.4%)	7.0%	(5.8%)	6.8%	(6.3%)	6.2%	(6.1%)	6.9%	(6.1%)	0.27	6.2%	(5.8%)	7.0%	(6.4%)	0.25
in-stent interpolated	4.7%	(5.3%)	5.3%	(6.2%)	6.2%	(6.0%)	6.0%	(6.0%)	5.0%	(5.7%)	6.1%	(6.0%)	0.09	5.4%	(5.7%)	5.7%	(6.1%)	0.67
6-month stenosis, %*																		
in-stent averaged	36.0%	(18.1%)	32.7%	(12.2%)	34.2%	(16.3%)	35.5%	(16.5%)	34.5%	(15.7%)	34.9%	(16.3%)	0.81	35.1%	(17.1%)	34.3%	(14.8%)	0.67
in-stent interpolated	34.3%	(19.0%)	30.5%	(12.9%)	32.3%	(17.4%)	34.1%	(16.9%)	32.6%	(16.5%)	33.2%	(17.1%)	0.73	33.3%	(18.2%)	32.6%	(15.4%)	0.72
in-segment averaged	38.7%	(16.0%)	34.3%	(10.7%)	36.9%	(15.1%)	37.1%	(15.0%)	36.7%	(14.0%)	37.0%	(15.0%)	0.84	37.8%	(15.5%)	35.9%	(13.4%)	0.25
in-segment interpolated	37.1%	(16.6%)	32.2%	(11.3%)	35.0%	(16.0%)	35.7%	(15.4%)	34.8%	(14.5%)	35.4%	(15.7%)	0.75	36.0%	(16.3%)	34.2%	(13.8%)	0.27
Acute Gain [B]-[A]	2.05	(0.47)	1.99	(0.51)	2.06	(0.48)	2.08	(0.54)	2.02	(0.49)	2.07	(0.51)	0.32	2.05	(0.48)	2.04	(0.53)	0.80
Late loss [B]-[C]*	1.07	(0.54)	0.92	(0.36)	1.00	(0.52)	1.10	(0.53)	1.00	(0.59)	1.05	(0.66)	0.36	1.04	(0.53)	1.02	(0.47)	0.81
Net gain [A]-[C]*	1.04	(0.58)	0.98	(0.60)	1.03	(0.68)	1.07	(0.63)	1.01	(0.59)	1.05	(0.66)	0.54	1.03	(0.61)	1.03	(0.64)	0.91
Late loss index*	0.53	(0.24)	0.50	(0.23)	0.50	(0.28)	0.54	(0.29)	0.52	(0.23)	0.52	(0.28)	0.85	0.51	(0.26)	0.52	(0.26)	0.73

Table 12. Quantitative coronary angiography data and derived vessel measurements (all lesions, n=359; *for lesions with completed follow up n=328). CoCr = cobalt chromium, SS = stainless steel, PCI =percutaneous coronary intervention

4.2 Endpoints

The primary endpoint of binary angiographic restenosis (50% or greater stenosis at 6 months) is reported in Table 13. In-segment average restenosis across all groups was 19.1% (95%CI: 14.7% to 24.2%) based on the averaged reference diameter. Numerically, the results vary according to the whether the interpolated or averaged reference diameter is used but this does not affect the primary endpoint. For the comparison between placebo and prednisolone, by averaged reference diameter, restenosis rates were 19.7% vs. 20.0% respectively, p=1.00 and, by interpolated reference diameter, 18.9% vs. 16.8% respectively, p=0.65. For the comparison between stainless steel and cobalt chromium stents, by averaged reference diameter, restenosis rates were 21.6% vs. 18.0% respectively, p=0.46 and, by interpolated reference diameter, 19.6% vs. 15.8% respectively, p=0.44. Overall, there was no difference in restenosis between treatment groups.

There were six additional restenosis episodes when the averaged reference diameter was used to calculate the stenosis diameter within the stented segment at follow up. The difference between the diameter stenosis when the average reference diameter was used compared to the interpolated reference diameter ranged from 2-7% (Table 15). This did not translate into additional clinical events; none had target lesion revascularisation within the follow up period.

The primary analysis was performed on an individual patient basis with one lesion chosen as the primary target lesion (first lesion treated). Table 14 shows the analysis for all lesions treated and in keeping with the primary analysis there was no statistically significant difference in the primary outcome. This is demonstrated graphically in the cumulative distribution curves for all lesions (Figures 14-17). They are also almost superimposed for both the drug and stent comparisons and the findings are similar whether diameter stenosis or minimal luminal diameter is used.

There were no clinically important differences in any other study endpoints, adverse or serious adverse events (Table 13). Both deaths that occurred were cardiac deaths. In one case, a patient presented again with acute pulmonary oedema secondary to an ACS and in the other case, a patient died suddenly whilst travelling but had been to see the general practitioner with recurrent anginal pains in the week prior to this.

There was, however, significant variation within the individual treatment combinations (varying from 11.7% to 26.4%) and a significant interaction was identified within a general-linear model. For in-stent average restenosis of target lesions the log-odds findings (x) were:

$$x = -2.024 + 0.804.drug + 0.999.stent - 1.555.drug{\cdot}stent$$

$p<0.001$ $p=0.096$ $p=0.039$ $p=0.015$

where *drug* is an indicator variable for prednisolone, *stent* is an indicator for stainless steel stent and *drug.stent* is the interaction term

for *stent* and *drug* combined. Findings were qualitatively similar, regardless of the restenosis definition taken for target lesions or use of hierarchical models including all treated lesions. Analysis of stenosis percentage (*y*) using a general linear model finds no suggestion of interaction.

$y = 33.40 + 3.11.drug + 3.20.stent - 5.82.drug \cdot stent$

p<0.001 p=0.26 p=0.25 p=0.12

Again, findings were qualitatively similar, regardless of the restenosis definition taken for target lesions or use of hierarchical models including all treated lesions. The explanation for these findings is apparent in the comparison of cumulative stenosis rates comparing the treatment combinations (Figures 18-20). Although there is no apparent difference over much of the distribution, there are apparent differences at the 40-50% stenosis point (leftward shift with the cobalt chromium/placebo and stainless steel/prednisolone group). Thus the finding may be an artefact of selectively dichotomising a continuous outcome. At this level of stenosis, this difference may not be of clinical importance. At the tail end with more severe stenoses, the curves seem to converge again except with the cobalt chromium/placebo group. There were fewer patients in this group and this therefore may just be a chance finding.

	Placebo, n=145				Prednisolone, n=170				Drug			Stent		
	SS, n=80		CoCr, n=65		SS, n=80		CoCr, n=90		Placebo	Pred.		SS	CoCr	
	Count	%	Count	%	Count	%	Count	%	%	%	p	%	%	p
Primary endpoint*														
Restenosis (by any measure)	19	(26.4%)	7	(11.7%)	13	(17.1%)	18	(22.8%)	19.7%	20.0%	1.00	21.6%	18.0%	0.46
in-segment averaged	19	(26.4%)	7	(11.7%)	13	(17.1%)	18	(22.8%)	19.7%	20.0%	1.00	21.6%	18.0%	0.46
in-segment interpolated	18	(25.0%)	7	(11.7%)	11	(14.5%)	15	(19.0%)	18.9%	16.8%	0.65	19.6%	15.8%	0.44
Secondary endpoints														
Target lesion revascularisation	9	(11.2%)	1	(1.5%)	6	(7.5%)	5	(5.6%)	6.9%	6.5%	1.00	9.4%	3.9%	0.07
Target vessel revascularisation	9	(11.2%)	2	(3.1%)	6	(7.5%)	6	(6.7%)	7.6%	7.1%	1.00	9.4%	5.2%	0.19
Any endpoint or SAE	20	(25.0%)	8	(12.3%)	13	(16.3%)	20	(22.2%)	19.3%	19.4%	1.00	20.6%	18.1%	0.67
MACCE														
composite	10	(12.5%)	2	(3.1%)	6	(7.5%)	6	(6.7%)	8.3%	7.1%	0.83	10.0%	5.2%	0.14
death	1	(1.3%)	0	(0.0%)	0	(0.0%)	1	(1.1%)	0.7%	0.6%	1.00	0.6%	0.6%	1.00
MI	1	(1.3%)	1	(1.5%)	0	(0.0%)	1	(1.1%)	1.4%	0.6%	0.60	0.6%	1.3%	0.62
CVA	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0.0%	0.0%	-	0.0%	0.0%	-
Target vessel revascularisation	9	(11.3%)	2	(3.1%)	6	(7.5%)	6	(6.7%)	7.6%	7.1%	1.00	9.4%	5.2%	0.19

Table 13. Primary analysis of study events for the 315 patients. Count data shown as: count (%); comparisons: group %, Fisher's exact test.* Analysed as target lesion (i.e. one lesion per patient), 287 patients completed final follow-up angiography (stainless steel (SS)/placebo, n=72; cobalt chromium (CoCr) /placebo, n=60; SS/prednisolone (pred), n=76; CoCr/prednisolone, n=79). MACCE, major adverse cardiovascular cerebrovascular events.

	Placebo, N=149				Prednisolone, N=179				Drug			Stent		
	SS, n=80		CoCr, n=69		SS, n=87		CoCr, n=92		Placebo	Pred.		SS	CoCr	
	Count	%	Count	%	Count	%	Count	%	%	%	p	%	%	p
Restenosis (by any measure)+	19	(23.8%)	7	(10.1%)	14	(16.1%)	20	(21.7%)	17.4%	19.4%	0.78	19.8%	16.8%	0.57
in-segment averaged	19	(23.8%)	7	(10.1%)	14	(16.1%)	20	(21.7%)	17.4%	19.4%	0.78	19.8%	16.8%	0.57
in-segment interpolated	18	(22.5%)	7	(10.1%)	12	(13.8%)	17	(18.5%)	16.8%	16.2%	1.00	18.0%	14.9%	0.46
in-stent averaged	19	(23.8%)	7	(10.1%)	12	(13.8%)	20	(21.7%)	17.4%	17.9%	1.00	18.6%	16.8%	0.77
in-stent interpolated	18	(22.5%)	7	(10.1%)	10	(11.5%)	17	(18.5%)	16.8%	15.1%	0.76	16.8%	14.9%	0.65
Revascularisation*														
Target lesion	9	(10.1%)	1	(1.4%)	7	(7.6%)	6	(5.8%)	6.1%	6.6%	1.00	8.8%	3.9%	0.08
Target vessel	10	(11.2%)	2	(2.7%)	7	(7.6%)	7	(6.7%)	7.4%	7.1%	1.00	9.4%	5.1%	0.15

Table 14. Angiographic and clinical restenosis rates for all lesions with angiographic follow up (n=328). Count data shown as: count (%); comparisons: group %, Fisher's exact test.* For revascularisation, clinical follow up available for all patients (359 lesions; stainless steel (SS)/placebo, n=89; cobalt chromium (CoCr) /placebo, n=74; SS/prednisolone (pred), n=92; CoCr/prednisolone, n=104).

Diameter stenosis (%) average reference diameter	Diameter stenosis (%) interpolated reference diameter	Difference (%)
51	48	3
50	48	2
51	49	2
52	47	5
51	49	2
51	44	7

Table 15. Diameter stenosis in six patients where there was binary angiographic restenosis using the averaged reference diameter but not the interpolated reference diameter.

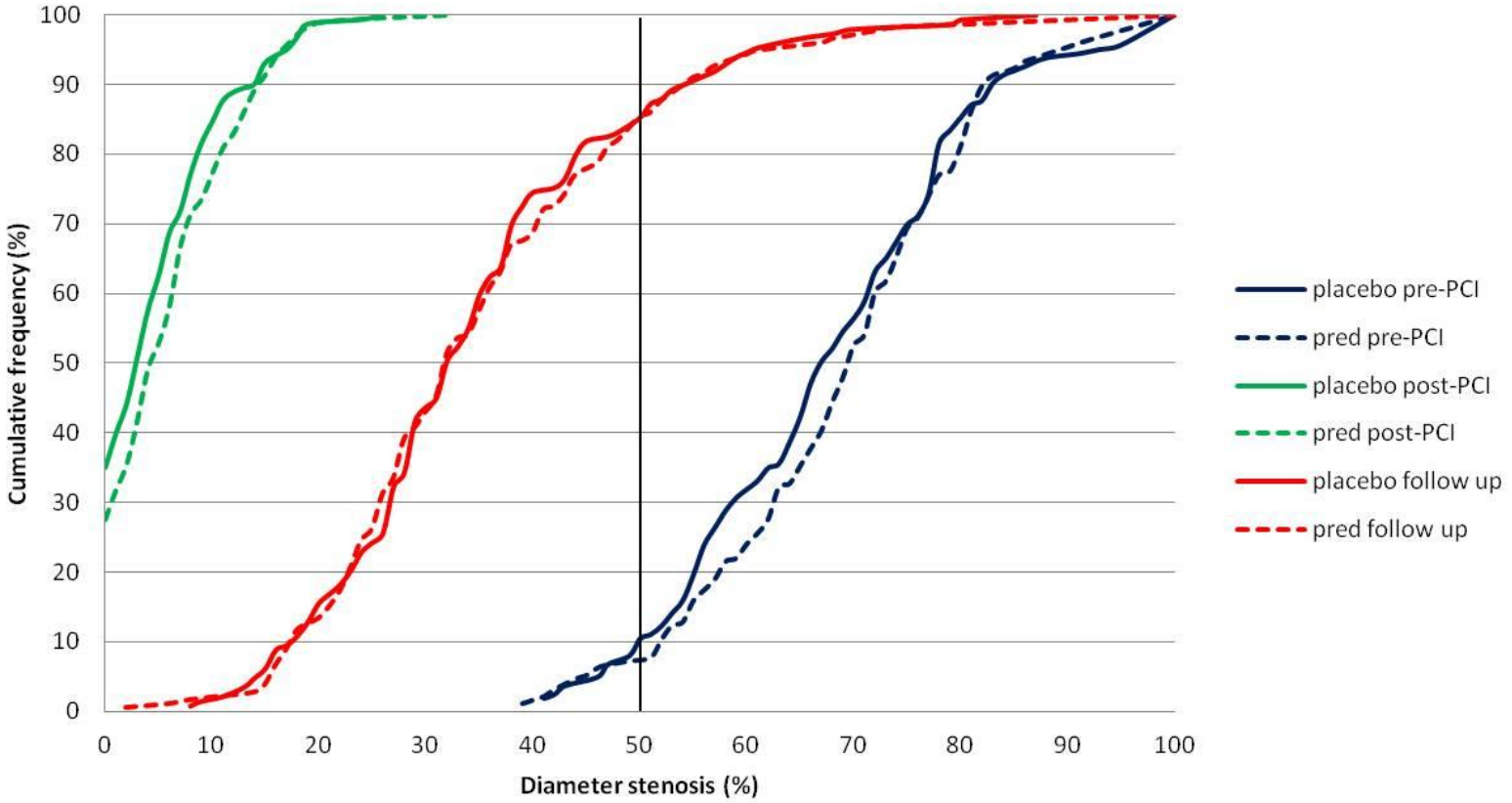


Figure 14. Graph showing cumulative distribution curves diameter stenosis using the interpolated reference diameter before and after percutaneous coronary intervention (PCI) and at follow-up for placebo and prednisolone (pred).

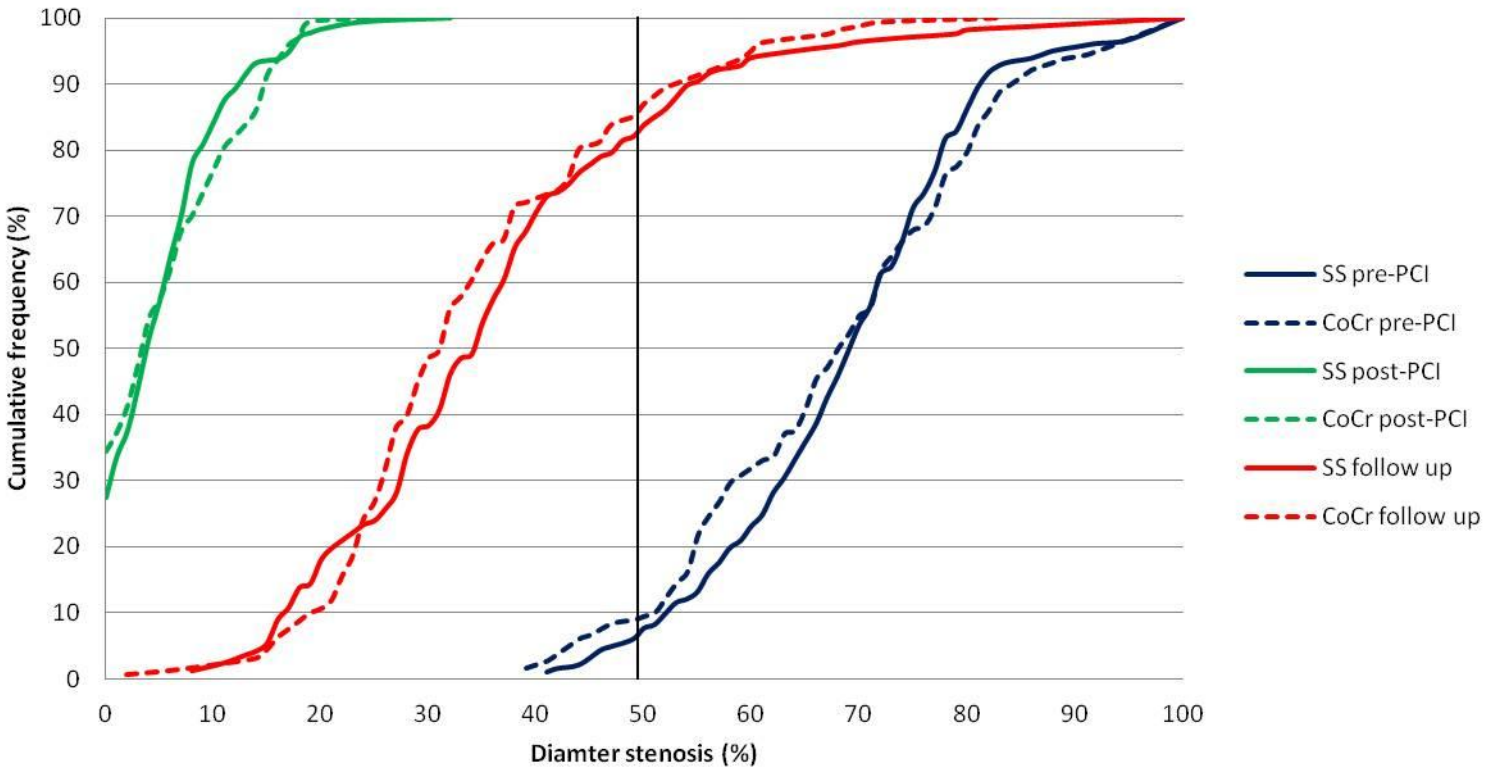


Figure 15. Graph showing cumulative distribution curves of diameter stenosis before and after percutaneous coronary intervention (PCI) and at follow-up for stainless steel (SS) and cobalt chromium (CoCr) stents.

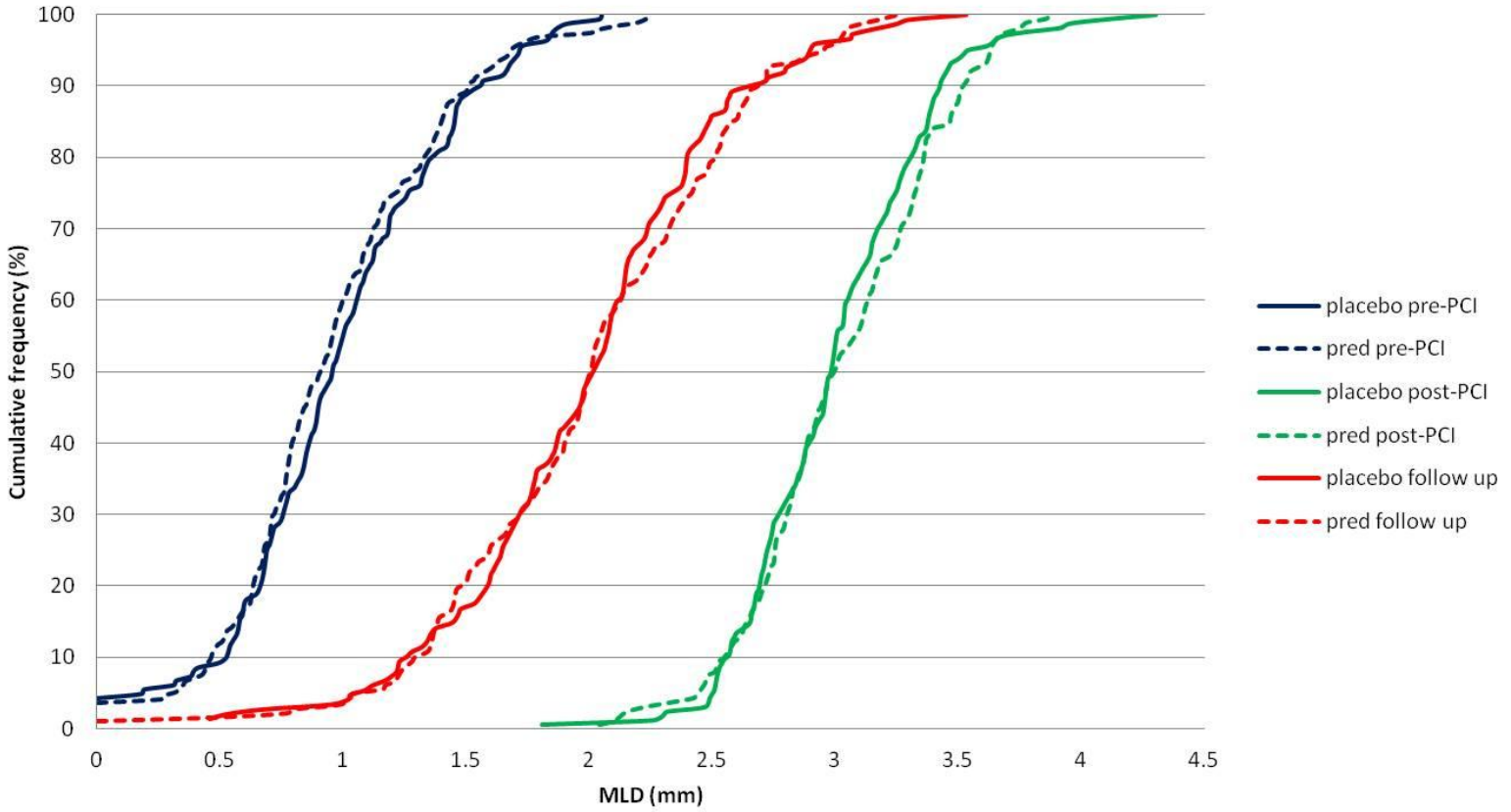


Figure 16. Graph showing cumulative distribution curves of minimal luminal diameter (MLD) before and after percutaneous coronary intervention (PCI) and at follow-up for placebo and prednisolone (pred).

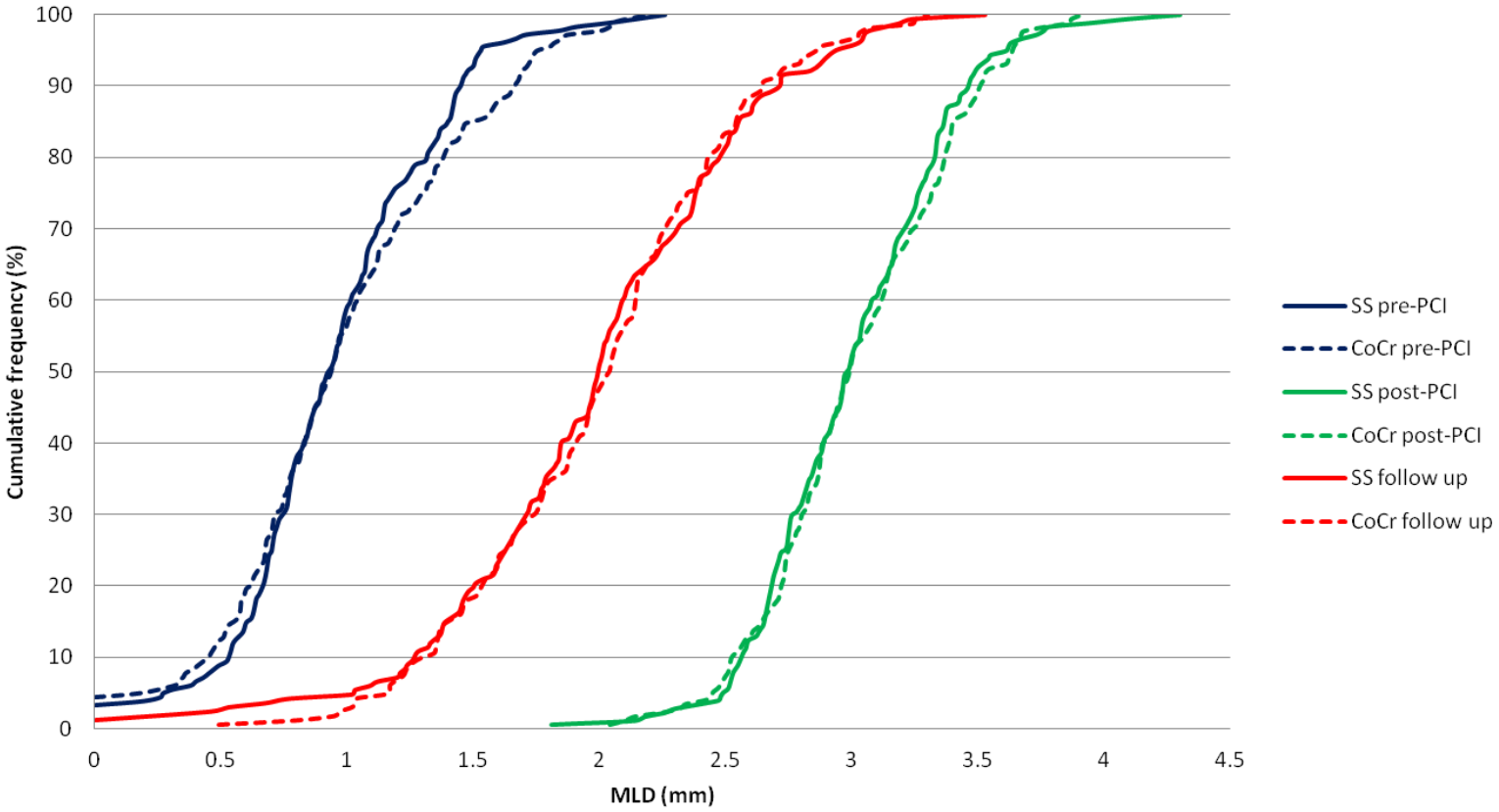


Figure 17. Graph showing cumulative distribution curves of minimal luminal diameter (MLD) before and after percutaneous coronary intervention (PCI) and at follow-up for stainless steel (SS) and cobalt chromium (CoCr) stents.

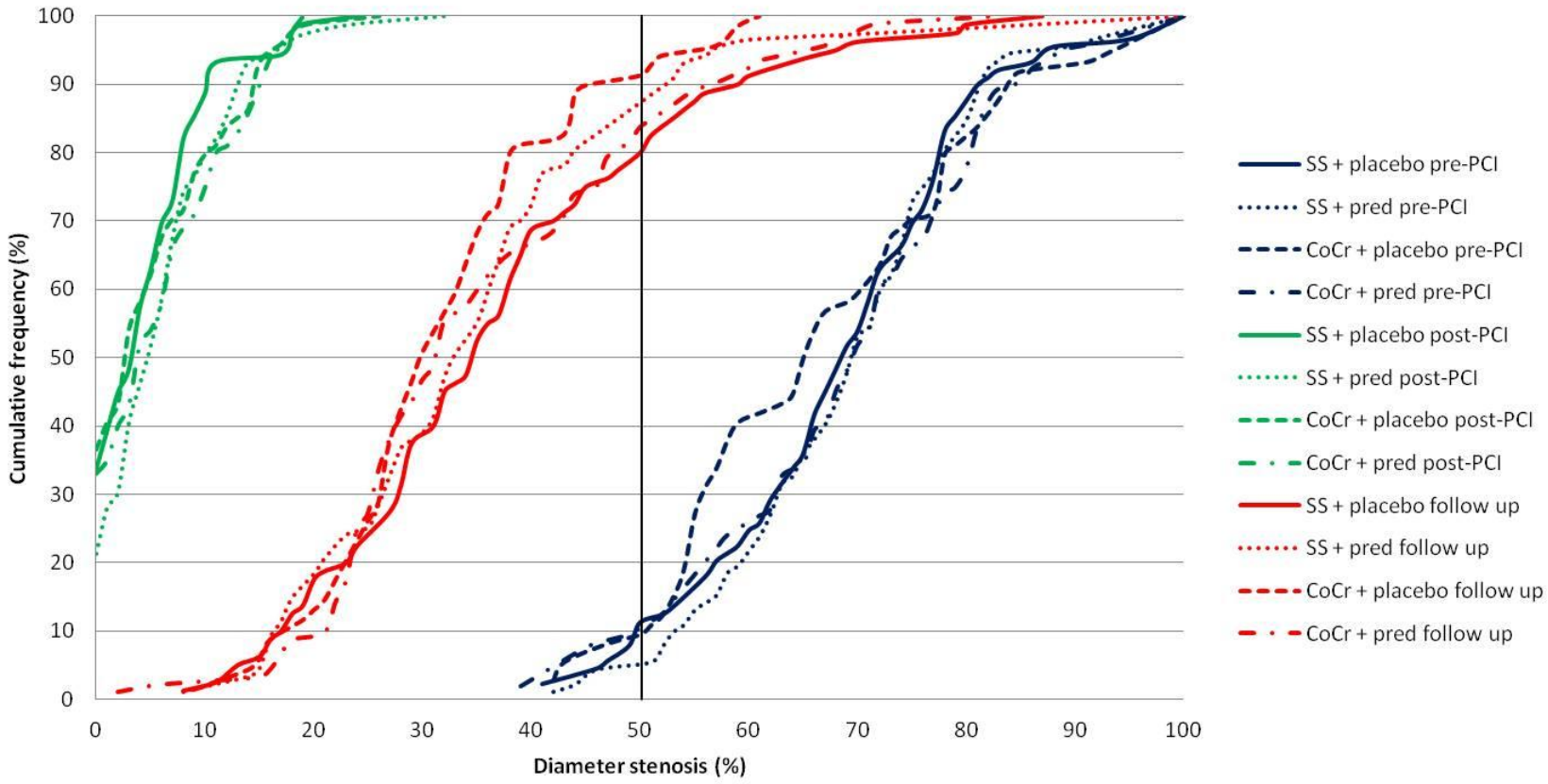


Figure 18. Graph showing cumulative distribution curves of diameter stenosis using the interpolated reference diameter before and after percutaneous coronary intervention (PCI) and at follow-up for all four possible study combinations. SS = stainless steel, CoCr = cobalt chromium, pred = prednisolone.

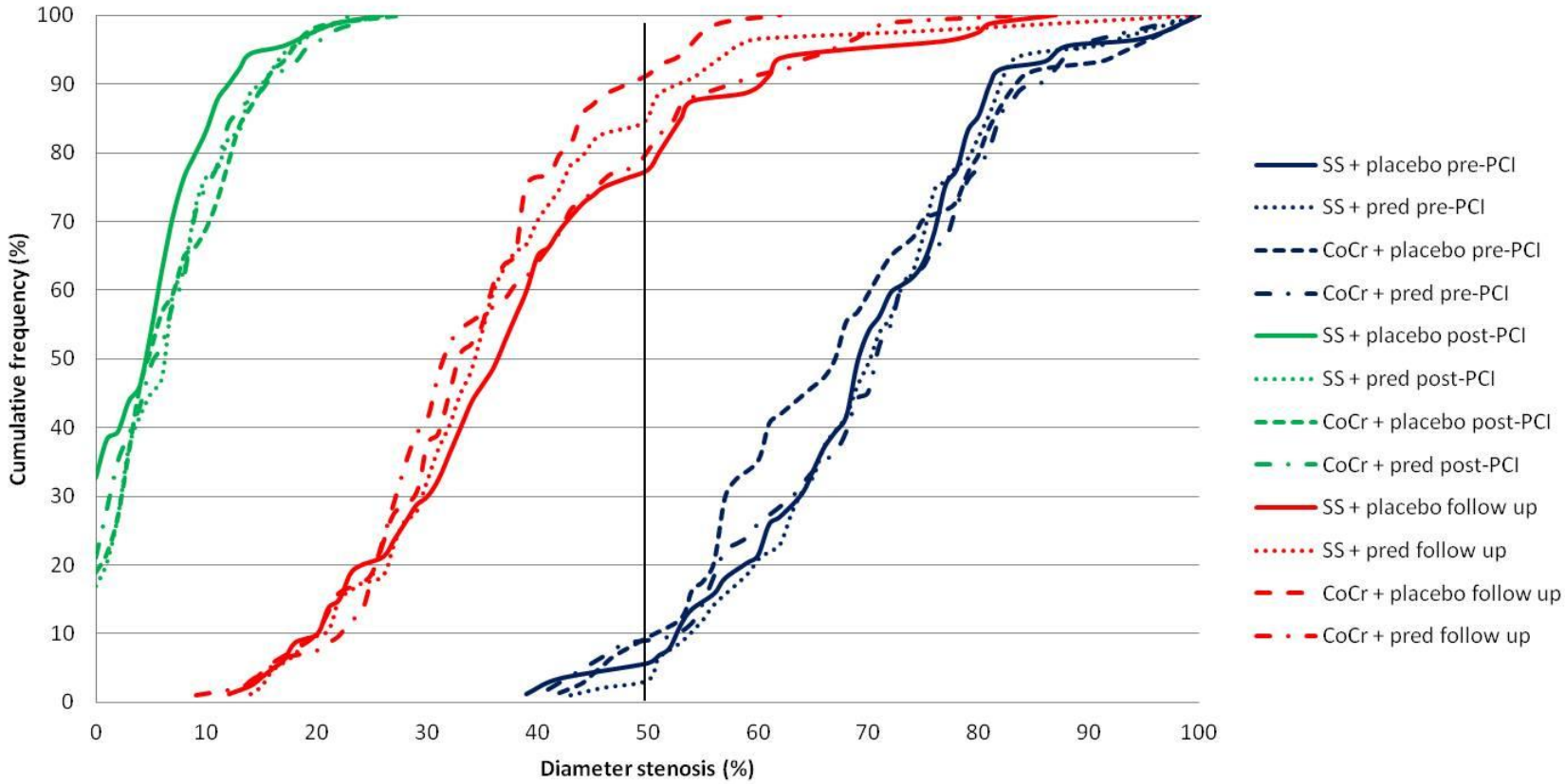


Figure 19. Graph showing cumulative distribution curves of diameter stenosis using the averaged reference diameter before and after percutaneous coronary intervention (PCI) and at follow-up for all four possible study combinations. SS = stainless steel, CoCr = cobalt chromium, pred = prednisolone.

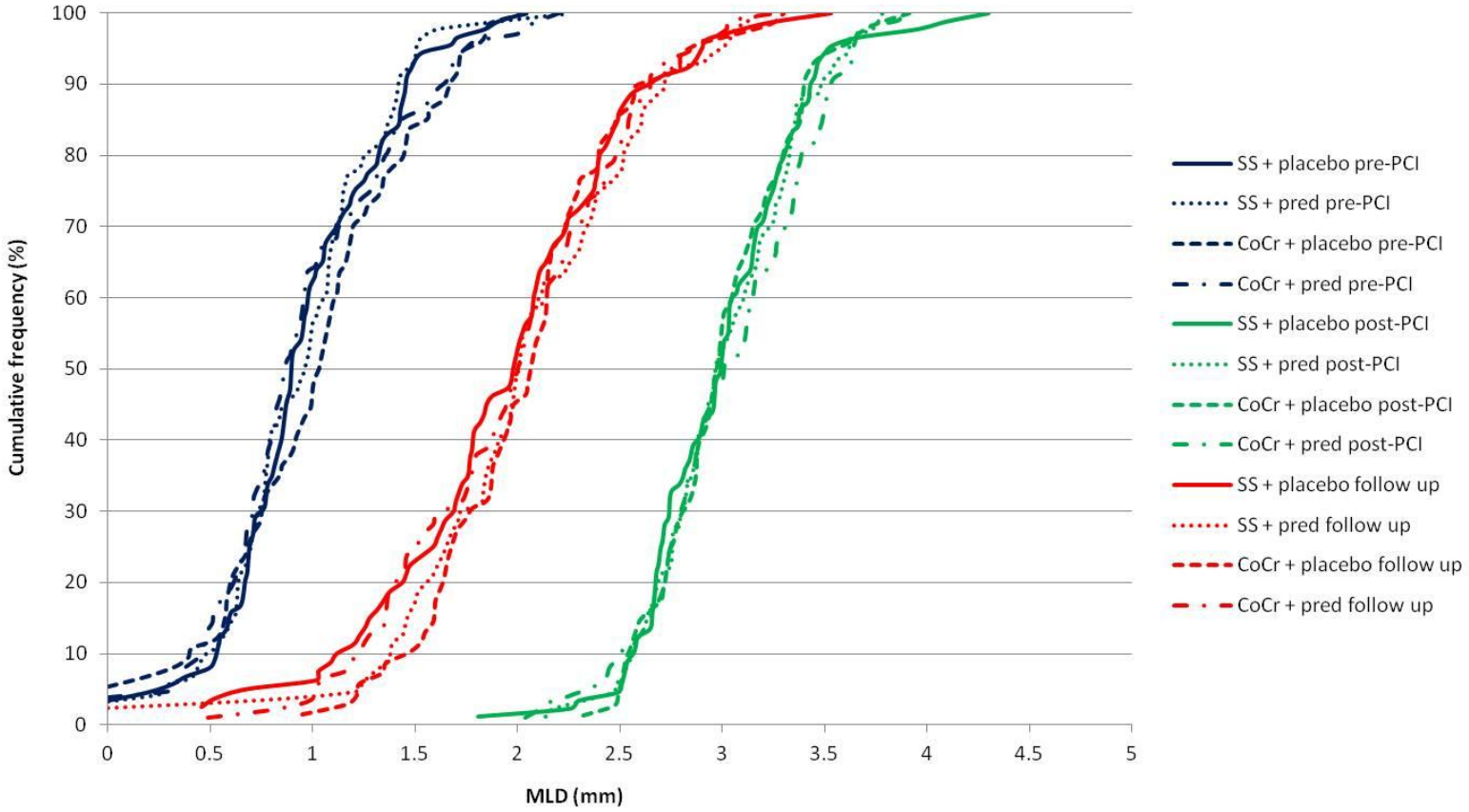


Figure 20. Graph showing cumulative distribution curves of minimal luminal diameter (MLD) before and after percutaneous coronary intervention (PCI) and at follow-up for all four possible study combinations. SS = stainless steel, CoCr = cobalt chromium, pred = prednisolone.

4.3 Types of restenosis

Restenosis has been classified according to whether it is focal (type I), diffuse intra-stent (type II), diffuse proliferative (type III) or occlusive (type IV) (Figure 21) (see section 1.2). Increasing TLR is seen with increasing class of restenosis (35) .

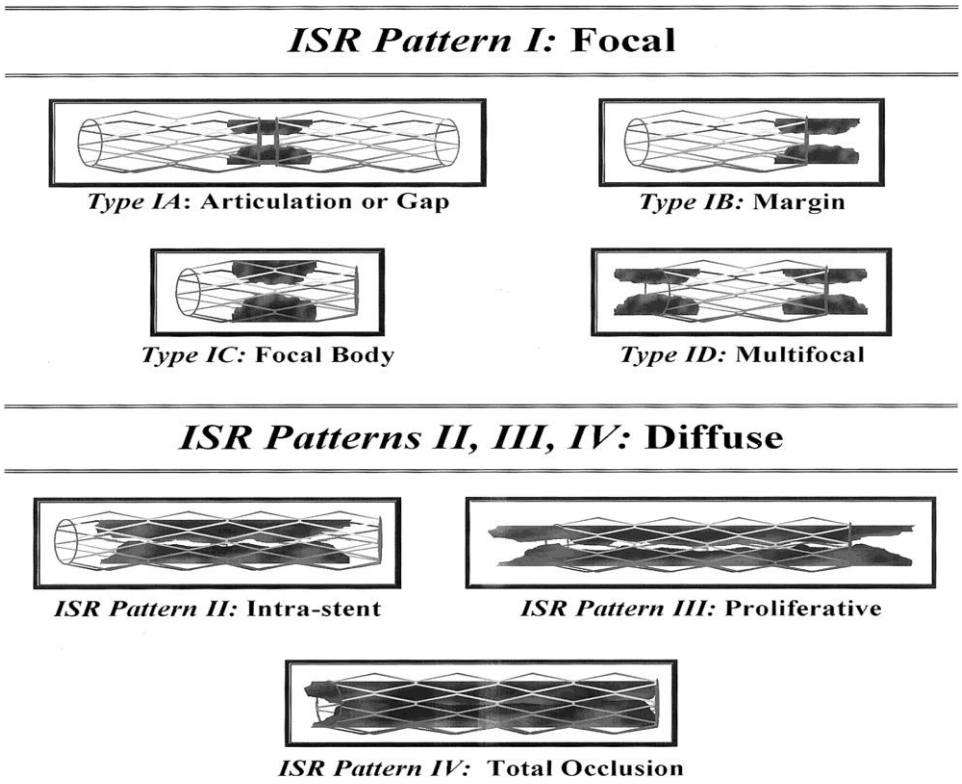


Figure 21. Schematic image of 4 patterns of introduced classification of ISR in relation to previous dichotomous description of focal vs. diffuse ISR. Pattern I contains 4 types (A-D). Patterns II through IV are defined according to geographic position of ISR in relation to previously implanted stent. Reproduced with permission from Mehran R et al. Circulation. 1999;100:1872-1878.

Binary angiographic restenosis occurred in 60 lesions (using averaged reference diameter). Of these, type I restenosis occurred in 39 (65%), type II

in 14 (23.3%), type III in 5 (8.3%) and type IV in 2 (3.3%). There was no difference in type of restenosis between placebo and prednisolone (Table 16). There was a difference in the type of restenosis between the stents which was mainly because of a difference in the focal (type I) subgroups. Within the stainless steel group, there were more restenostic lesions at the margins of the stent whilst restenosis occurred more frequently within the body of the stent in the cobalt chromium group. There is no clear explanation for this but the cobalt chromium stents were newer stents with more contemporary balloon technology and potentially less balloon overhang at the margins of the stent and therefore less injury to the vessel.

Although not statistically significant, there were more lesions with proliferative or occlusive restenosis (class III/IV) within the stainless steel group (Table 17). Of the lesions with these types of stenosis the stented segment was >30mm in four and they were all in the stainless steel group.

	Placebo (n=26)		Prednisolone (n=34)		p
Class of restenosis					0.41
I	17	(65.4%)	22	(64.7%)	
A	0	(0.0%)	0	(0.0%)	
B	8	(30.8%)	7	(20.6%)	
C	8	(30.8%)	13	(38.2%)	
D	1	(3.8%)	2	(5.9%)	
II	5	(19.2%)	9	(26.5%)	
III	4	(15.4%)	1	(2.9%)	
IV	0	(0.0%)	2	(5.9%)	
Diffuse (Class II,III,IV)	9	(34.6%)	12	(35.3%)	1.00
Diffuse proliferative/occlusive (Class III/IV)	4	(15.4%)	3	(8.8%)	0.45

Table 16. Type of restenosis, comparison between placebo and prednisolone.

	Stainless steel (n=33)		Chromium cobalt (n=27)		p
Class of restenosis					0.01
I	21	(63.6%)	18	(66.7%)	
A	0	(0.0%)	0	(0.0%)	
B	13	(39.4%)	2	(7.4%)	
C	7	(21.2%)	14	(51.9%)	
D	1	(3.0%)	2	(7.4%)	
II	6	(18.2%)	8	(29.6%)	
III	4	(12.1%)	1	(3.7%)	
IV	2	(6.1%)	0	(0.0%)	
Diffuse (Class II,III,IV)	12	(36.4%)	9	(33.3%)	1.00
Diffuse proliferative/occlusive (Class III/IV)	6	(18.2%)	1	(3.7%)	0.12

Table 17. Type of restenosis, comparison between stainless steel and cobalt chromium stents.

4.4 Bleeding and hyperglycaemia

Overall there was no difference in any bleeding episode compared to placebo 7.6% vs. 5.5% for placebo, p=0.50. Almost all of these were minimal bleeding episodes, mainly related to femoral access (2.9% vs. 2.8% for placebo) at the time of the procedure. The minor bleeding episodes occurred in the prednisolone group. In one case, a patient had spontaneous frank haematuria after PCI. The patient was haemodynamically stable and had been on Abciximab which was stopped. Haemoglobin and platelet counts were within normal limits and the patient was discharged with outpatient investigations revealing the presence of renal stones. In the other case also in the prednisolone group, one patient was readmitted two months post procedure and transfused two units of packed cells for symptomatic iron deficiency anaemia. This was subsequently attributed to peptic ulcer disease. The only major bleeding episode occurred in the placebo group where one patient experienced bleeding per rectum with a drop in haemoglobin of >5g/dl requiring transfusion of three units of packed red blood cells. This occurred during the same hospital admission as the PCI procedure and study medication was stopped. The source of the bleeding was subsequently found to be rectal carcinoma that was successfully treated.

With regards to hyperglycaemia, significantly more patients had home blood glucose monitoring levels greater than 11mmol/l in the prednisolone group, 39(22.9%) vs. 10(6.9%) for placebo, p<0.01 during follow up. This was evident both in patients known to have diabetes 12(7.1%) vs. 4(2.8%) for placebo or not 27(15.9%) vs. (4.1%) for placebo. In the majority of cases, dietary advice and reassurance was all that was necessary for these patients

and there was no significant difference between the groups in terms of need for additional oral hypoglycaemic therapy, insulin or need for study medication to be stopped (Figure 22).

	Placebo, n=145		Prednisolone, n=170		p
Any bleeding episode	8	(5.5%)	13	(7.6%)	0.50
Bleeding type					0.40
Insignificant	7	(4.8%)	11	(6.5%)	
Minor	0	(0.0%)	2	(1.2%)	
Major	1	(0.7%)	0	(0.0%)	
Bleeding site					0.69
Access site	5	(3.5%)	6	(3.5%)	
Femoral	4	(2.8%)	5	(2.9%)	
Radial	1	(0.7%)	1	(0.6%)	
ENT	2	(1.4%)	3	(1.8%)	
Genitourinary	0	(0.0%)	1	(0.6%)	
Gastrointestinal	1	(0.7%)	3	(1.8%)	

Table 18. Bleeding events, comparison between prednisolone and placebo. ENT = Ear, Nose, Throat (all events were minor epistaxis episodes not requiring intervention (see text for detail).

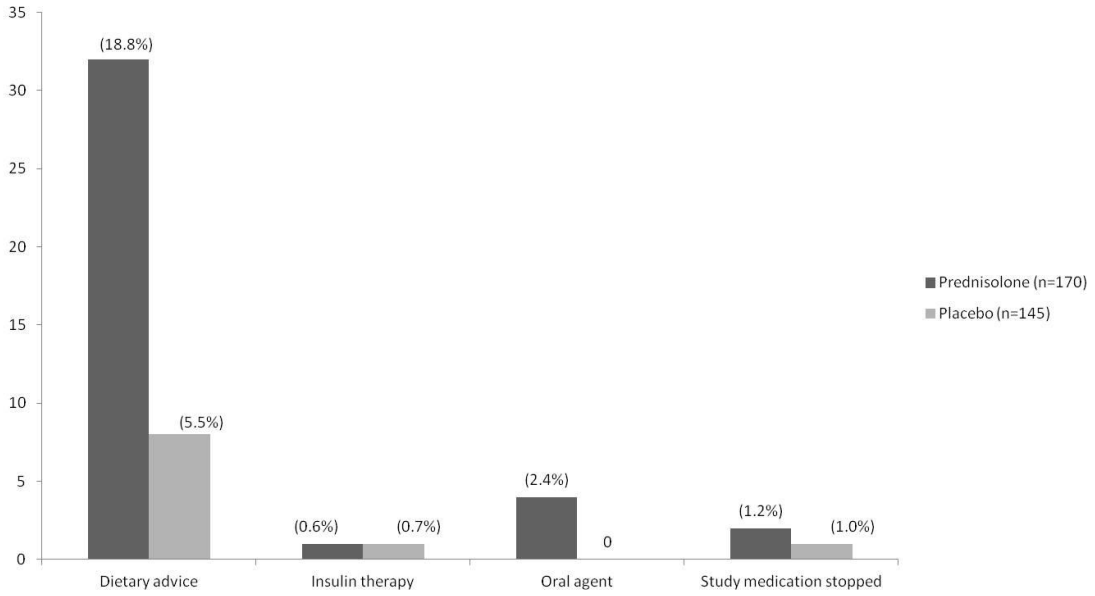


Figure 22. Interventions for hyperglycaemia episodes during follow up.

4.5 Biomarkers

Hs-CRP was assayed on the Siemens Advia 2400 Chemistry analyser (Siemens Healthcare Diagnostics, Frimley, UK) using the Siemens wide range CRP latex-enhanced immunoturbidimetric assay. The analytical range for hs-CRP was 0.03–[156-164] mg/L; the inter-assay and intra-assay variabilities were 4.9–7.8% from 2.25– 49.96 mg/L and 3.2–5.2% from 2.25–49.96 mg/L respectively. The normal range for this hs-CRP assay is 0-5mg/l.

Table 19 shows the mean hs-CRP values at five points during the trial. There was some evidence of prednisolone suppressing hs-CRP response at day 7 (-5.98 mg/L, 95%CI: -8.35 to -3.61, p<0.001) and the suggestion of a small rebound at day 30 (2.71mg/L, 95%CI: 0.78 to 4.65, p=0.006).

Glycated haemoglobin (Hb_{A1c}) was also monitored at different points during the trial. There was a statistically significant increase in this parameter within the prednisolone group at 30 days but this returned back to baseline at six

months. This did not equate to any clinically important differences between treatments during the trial (Table 19).

The majority of patients in whom hs-CRP samples were available or suitable for analysis had levels within the normal range prior to PCI (71%). Only a small proportion of these (28 patients), still had elevated levels at day 7 (Figure 23).

4.5.1 Raised hs-CRP before procedure and restenosis

In those with angiographic follow up, there was no significant difference in restenosis between patients with raised hs-CRP before PCI (11 events out of 71 cases) compared to those without (43 events out of 202 cases), odds ratio (OR) 0.68, 95%CI 0.33-1.40, p=0.29 using the averaged reference diameter. Using binary logistic regression and adjusting for significant co-variates defined as p<0.2 on univariate analysis or known risk factors for restenosis (Table 20), this remained non-significant, OR 0.56, 95%CI 0.26-1.22, p=0.14.

For the patients (n=86) with raised CRP to begin with, 71 completed angiographic follow up (placebo, n=33 and prednisolone, n=38). Binary angiographic restenosis rates were 15.2% (n=5) for placebo compared to 15.8% (n=6) for prednisolone, p=1.00 using the averaged reference diameter and 15.2% (n=5) for placebo compared to 13.2% (n=5) for prednisolone, p=1.00 using the interpolated reference diameter.

For this cohort, binary angiographic restenosis rates were 18.6% (n=8) for stainless steel compared to 10.7% (n=3) for cobalt chromium, p=0.51 using the averaged reference diameter and 16.3% (n=7) for stainless steel

compared to 10.7% (n=3) for cobalt chromium, p=0.73 using the interpolated reference diameter.

As there were fewer patients with high baseline hs-CRP levels, the values were categorised to assess for any trends using different cut-offs. Again, there was no significant association between hs-CRP and restenosis (Table 21).

4.5.3 Change in hs-CRP and restenosis

Of the 28 patients with normal CRP prior to PCI and raised post PCI, 25 received placebo and the binary angiographic restenosis rate in this group was 20.0% (using averaged reference diameter) which was in keeping with the overall results of the trial.

The trends in hs-CRP on an individual patient level are shown in the line graphs in Figure 24. For the placebo arm there is an overall upward trend in CRP levels (A and B) but for prednisolone treated patients (C and D), there is a downward trend and this is seen in both the patients who had binary angiographic restenosis and those who did not. Furthermore, the scatter plot in Figure 25 shows that there was no correlation between change in CRP and diameter stenosis (r=-0.09, p=0.17).

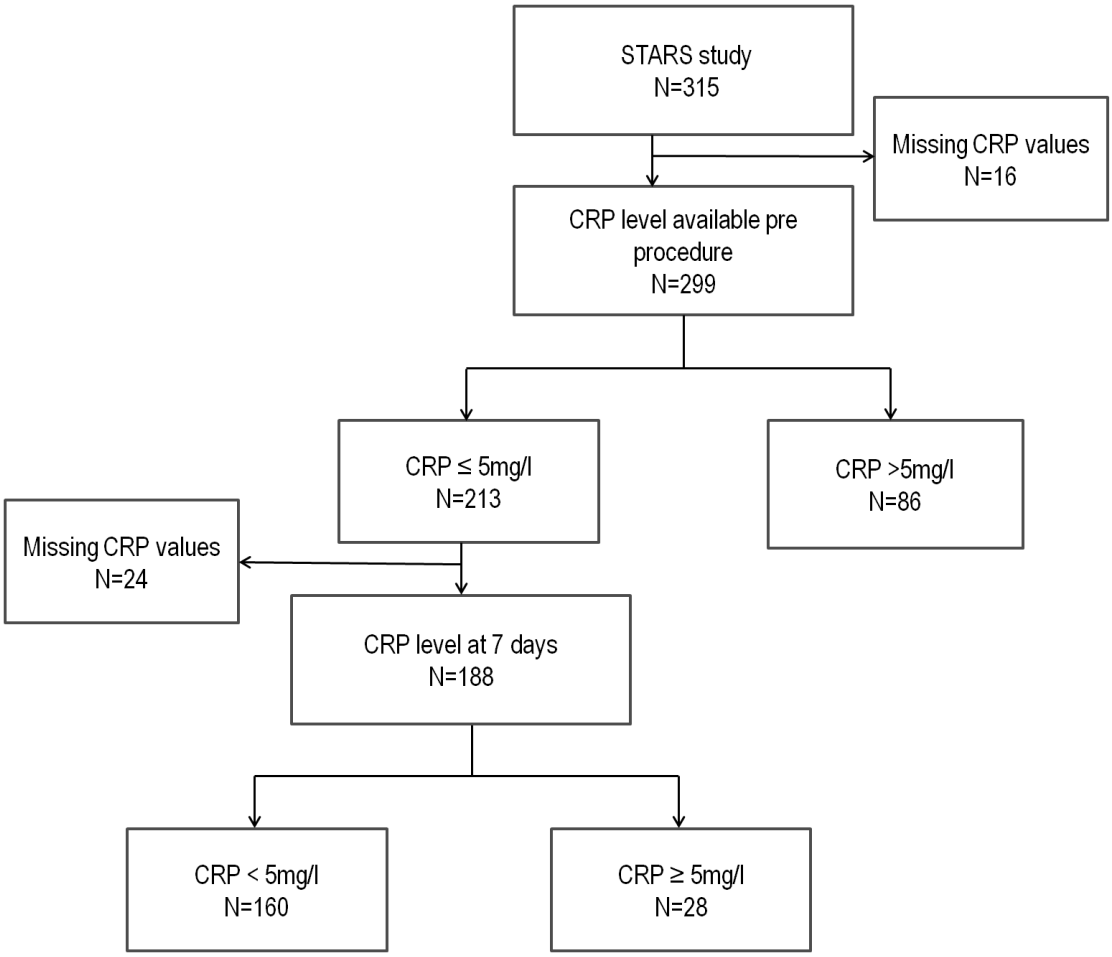


Figure 23. Flow chart depicting measurement of highly sensitive C-Reactive Protein (CRP) before and after percutaneous coronary intervention.

	Placebo				Prednisolone				Drug			Stent		
	CrCo		SS		CrCo		SS		Prednisolone-Placebo			SS-CrCo		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	95% CI		p	95% CI		p
hs-CRP, mg/L														
admission	6.31	(14.53)	8.32	(13.11)	5.39	(11.77)	6.36	(15.07)	-4.90	1.72	0.35	-1.73	4.83	0.35
pre-procedure	5.36	(12.77)	6.66	(10.50)	4.51	(11.32)	6.69	(15.19)	-3.56	2.53	0.74	-1.22	4.83	0.24
7 days	7.25	(9.38)	7.57	(16.14)	1.86	(6.99)	0.96	(3.01)	-8.35	-3.61	<0.001	-2.31	2.62	0.90
30 days	4.11	(9.85)	3.33	(6.38)	5.79	(6.56)	7.03	(9.43)	0.78	4.65	0.006	-1.79	2.12	0.87
6 months	1.48	(1.77)	3.29	(4.31)	2.45	(4.51)	4.36	(12.82)	-1.09	2.79	0.39	-0.15	3.69	0.07
Hb_{A1c}, %														
admission	5.75	(0.85)	5.86	(0.97)	5.83	(0.87)	5.71	(0.50)	-0.23	0.16	0.75	-0.21	0.18	0.88
30 days	5.72	(0.67)	5.75	(0.60)	6.01	(1.24)	5.95	(0.55)	0.05	0.44	0.016	-0.23	0.16	0.73
6 months	5.75	(0.67)	5.95	(0.83)	5.96	(1.14)	5.82	(0.51)	-0.17	0.24	0.75	-0.19	0.23	0.85
Time to 30d FU (d)	37.6	(104.5)	32.6	(6.9)	40.9	(79.0)	28.4	(41.6)	-15.1	15.2	1.00	-24.0	6.1	0.24
Time to 6m FU (d)	210	(37)	204	(37)	203	(34)	201	(28)	-12.9	3.0	0.22	-11.3	4.6	0.41

Table 19. Highly sensitive C-Reactive Protein (hs-CRP) and glycated haemoglobin (Hb_{A1c}) levels at different time points during the trial.

		Restenosis rate		Univariate				Multivariate			
Factor	Total, n	n	%	OR	95% CI		p	OR	95% CI		p
Female	41	12	(29.3%)	1.85	0.88	3.90	0.11	2.08	0.88	3.90	0.08
Diabetic	28	3	(10.7%)	0.46	0.13	1.57	0.21	0.65	0.18	2.37	0.52
CRP raised pre-PCI	71	11	(15.5%)	0.68	0.33	1.40	0.29	0.56	0.26	1.22	0.14
Ref. vessel <2.5mm	27	10	(37.0%)	2.67	1.15	9.19	0.02	2.55	1.01	6.42	0.05
Lesion length >20mm	39	15	(38.5%)	3.07	1.48	6.33	<0.01	2.09	0.90	4.84	0.09
Complex lesion	122	35	(28.7%)	2.62	1.44	4.75	<0.01	1.97	0.99	3.94	0.06

Table 20. Odds ratios (95% confidence intervals) for factors identified on univariate analysis with either p<0.2 or known risk factor for restenosis for all patients with angiographic follow up are shown and subsequent multivariate analysis using binary logistic regression.

	All patients	Restenosis rate					
Hs- CRP (mg/l)	n	n	%	OR	95% CI		p
<1.00	108	22	(20.4%)	1.06	0.58	1.95	0.84
1.00-1.99	39	10	(25.6%)	1.49	0.68	3.28	0.32
2.00-2.99	25	7	(28.0%)	1.66	0.66	4.21	0.28
3.00-4.99	31	4	(12.9%)	0.57	0.19	1.70	0.57
5.00-9.99	30	6	(20.0%)	1.02	0.39	2.62	0.97
>10.0	40	5	(12.5%)	0.54	0.20	1.44	0.22
	273	54					

Table 21. Univariate analysis for all patients with angiographic follow up and baseline (pre-procedural) hs-CRP levels showing restenosis rates and odds ratios (95% confidence intervals (CI) using different hs-CRP cut-off values.

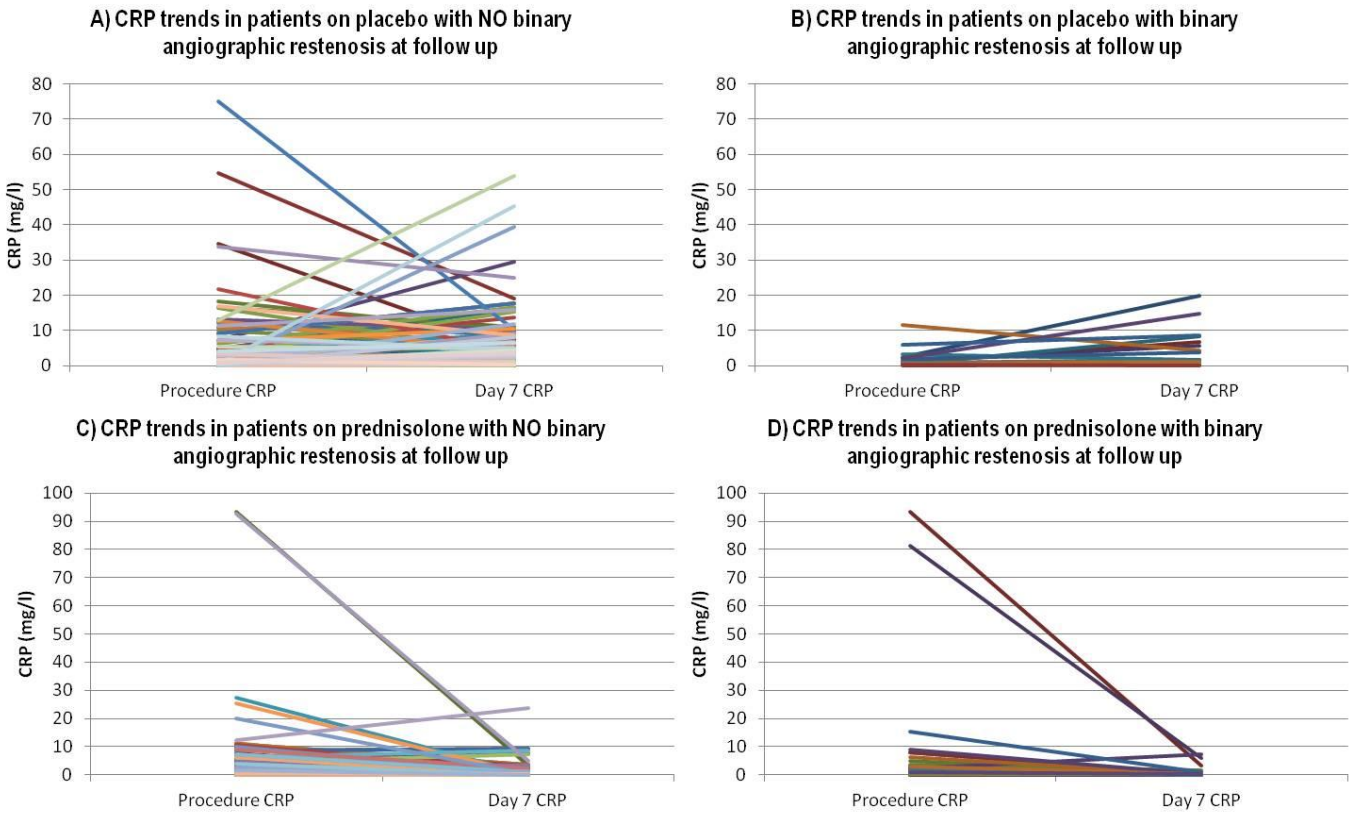


Figure 24. Relationship between CRP and binary angiographic restenosis on an individual patient basis. A and B are for participants in the placebo arm, and C and D in the prednisolone arm.

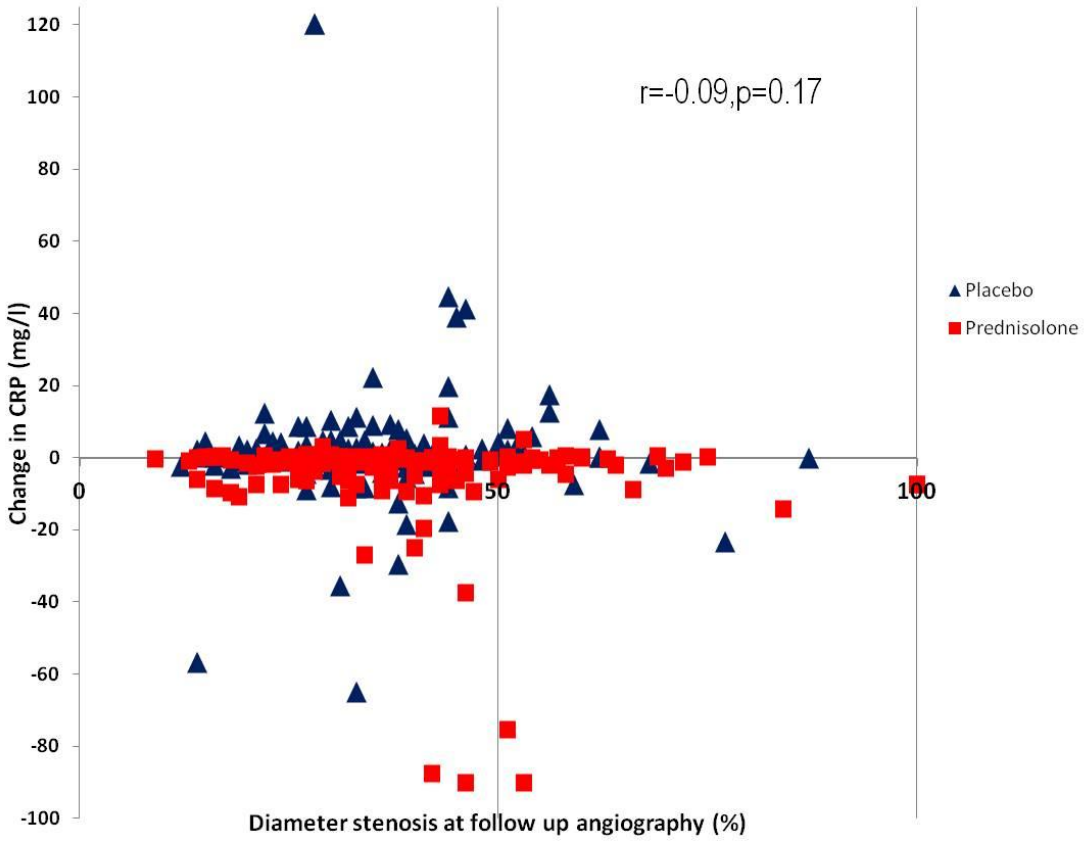


Figure 25. Relationship between change in CRP and restenosis at follow up.

4.6 Sirolimus eluting stents

Of the 315 patients who underwent a second randomisation, 30 had additional lesions where the operator implanted a Cypher ™ sirolimus-eluting stent. The mean age of participants was 60 years (range 39 to 74 years), 87% were male, 47% were elective PCI cases and the mean number of lesions treated was 1.14 (range 1 to 4). There were 16 patients in the placebo group and 14 patients in the prednisolone group. Groups were similar at baseline, there were no significant or important baseline differences comparing groups apart from the number of balloon inflations. (Tables 22- 23).

Reference and minimal luminal diameters, with derived levels of stenosis are shown for all lesions in Table 24. There were significant differences in the reference vessel diameters between the two groups, with smaller vessels treated in the placebo group. There was no evidence of difference in stenosis by any measure pre or post PCI, or at follow up. For all the lesions included (n=33, 28 with follow up angiography), acute gain was 1.75mm ± 0.48mm , late loss was 0.22mm ± 0.09mm and net gain was 1.47mm ± 0.46mm. Again, there was no difference between patients receiving prednisolone and those on placebo for these parameters. None of the patients had binary angiographic restenosis.

	Placebo, N=16		Prednisolone, N=14		p
Male	15	(93.8%)	5	(35.7%)	0.38
Age, y	62.3	(9.16)	58.2	(9.77)	0.25
Height, m	1.74	(0.11)	1.71	(0.07)	0.49
Weight, kg	82.6	(17.6)	84.6	(16.4)	0.75
Smoking status					0.59
never smoked	6	(37.5%)	6	(42.9%)	
ex-smoker	5	(31.2%)	6	(42.9%)	
current smoker	5	(31.2%)	2	(14.3%)	
History of hypertension	9	(56.2%)	7	(50.0%)	1.00
Family history of IHD	7	(43.0%)	9	(64.3%)	0.30
Previous MI	5	(31.2%)	2	(14.3%)	0.40
Previous CABG	1	(6.2%)	0	(0.0.%)	1.00
Previous PCI	2	(12.5%)	0	(0.0.%)	0.49
Previous TIA/CVA	0	(0.0.%)	0	(0.0.%)	-
History of PVD	2	(12.5%)	0	(0.0.%)	0.49
History of LVSD	1	(6.2%)	2	(14.3%)	0.59
Renal disease	0	(0.0.%)	0	(0.0.%)	-
Diabetes (I or II)	1	(6.2%)	1	(7.1%)	1.00
Hypercholesterolaemia	15	(93.8%	13	(92.9%)	1.00
Cholesterol, mmol/L	4.65	(1.13)	4.76	(1.48)	0.82
Creatinine value, µmol/L	95.6	(16.4)	90.7	(15.8)	0.42
Troponin, µg/L	0.40	(0.28)	0.44	(0.52)	0.88
Elective PCI	9	(56.2%)	5	(35.7%)	
ACS type					0.15
unstable angina	0	(0.0%)	3	(21.4%)	
non-STEMI	7	(43.8%)	5	(35.7%)	
STEMI	0	(0.0%)	1	(7.1%)	
GPIIb/IIIa type					0.72
none	7	(43.8%)	5	(35.7%)	
Abciximab	9	(56.2%)	9	(64.3%)	
Tirofiban	0	(0.0%)	0	(0.0%)	

Table 22. Baseline procedural data. Count data shown as: count (%); comparisons: Fisher's exact test. Numeric data shown as: mean (SD); comparisons: independent samples t-test.

IHD = Ischaemic heart disease, MI = Myocardial infarction, CABG = Coronary artery bypass grafting, PCI = Percutaneous coronary intervention, TIA = Transient Ischaemic attack, CVA = Cerebrovascular accident, PVD = Peripheral vascular disease, LVSD = Left ventricular systolic dysfunction, ACS = Acute coronary syndrome, GP IIb/IIIa = Glycoprotein IIb/IIIa inhibitor.

	Placebo, N=19		Prednisolone, N=14		p
Vessels treated					0.10
LAD	9	(47.4%)	9	(64.3%)	
Cx	5	(26.3%)	0	(0.0%)	
Int	1	(5.3%)	0	(0.0%)	
RCA	3	(15.8%)	5	(35.7%)	
AHA/ACC lesion type					0.08
A	0	(0.0%)	0	(0.0%)	
B1	4	(21.1%)	0	(0.0%)	
B2	9	(47.4%)	5	(35.7%)	
C	6	(31.6%)	9	(64.3%)	
Max balloon pressure, atm	16.0	(14.0-18.0)	16.0	(14.0-16.0)	0.87
No. of inflations	4.0	(3.0-8.0)	8.0	(4.0-10.0)	0.03
Total inflation time, s	57.0	(35.0-104.0)	95.0	(55.0-135.0)	0.20
Lesion length, mm	14.8	(10.8-23.7)	17.6	(12.0-33.6)	0.63
Stent length, mm	20.5	(18.0-28.0)	23.0	(18.0-38.0)	0.51

Table 23. Baseline procedural data. Count data shown as: count (%); comparisons: Fisher's exact test. Numeric data shown as: median (IQR); comparisons: independent samples Mann-Whitney U test. LMS = Left main stem, LAD = Left anterior descending, Cx = Circumflex, Int = Intermediate, RCA = Right coronary artery, SVG = Saphenous vein graft, ACC/AHA = American College of Cardiology/ American Heart Association.

	Placebo, N=19		Prednisolone,N=14		95% CI		p
Pre-PCI reference diameters, mm							
averaged	2.50	(2.43-2.63)	2.85	(2.76-3.22)			<0.01
interpolated	2.39	(2.31-2.61)	2.75	(2.53-3.15)			<0.01
Post-PCI reference diameters, mm							
averaged	2.53	(2.45-2.59)	2.99	(2.92-3.32)			<0.01
interpolated	2.54	(2.41-2.71)	3.04	(2.79-3.33)			<0.01
6-month PCI segment computer-derived							
averaged	2.46	(2.36-2.57)	2.96	(2.73-3.27)			<0.01
interpolated	2.46	(2.36-2.64)	2.89	(2.65-3.12)			<0.01
Minimum luminal diameters, mm							
Pre-PCI [A]	0.81	(0.34)	1.05	(0.47)	-0.53	0.05	0.10
Post PCI, in-stent [B]	2.50	(0.29)	2.89	(0.23)	-0.58	-0.20	<0.01
Follow up, in-stent [C]*	2.23	(0.28)	2.63	(0.23)	-0.60	-0.20	<0.01
Pre-PCI stenosis, %							
averaged	65.3	(58.1-68.5)	64.1	(60.6-72.4)			0.68
interpolated	64.0	(57.5-67.0)	63.5	(59.1-71.1)			0.65
Post-PCI stenosis, %							
in-stent averaged	2.4	(1.1-8.7)	7.2	(3.0-10.5)			0.24
in-stent interpolated	3.6	(1.5-7.7)	5.8	(1.6-9.0)			0.65
6-month stenosis, %							
in-stent averaged	8.0	(3.2-14.8)	12.4	(11.2-14.6)			0.17
in-stent interpolated	10.2	(6.1-13.4)	9.6	(5.6-11.7)			0.45
in-segment averaged	18.1	(16.0-19.8)	20.0	(16.1-24.4)			0.45
in-segment interpolated	17.6	(15.8-22.6)	18.5	(13.7-21.9)			0.77
Acute Gain [B]-[A]	1.69	(0.52)	1.83	(0.41)	-0.49	0.20	0.39
Late loss [B]-[C]	0.21	(0.08)	0.24	(0.11)	-0.18	0.04	0.33
Net gain [A]-[C]	1.38	(0.45)	1.60	(0.45)	-0.57	1.36	0.22
Late loss index	0.14	(0.08)	0.13	(0.06)	-0.05	0.06	0.92

Table 24. Vessel measurements for all lesions (N=33). *Follow up data, N=28 (Placebo, N=16; Prednisolone, N=14). Median (interquartile range) for non parametric comparisons, otherwise mean (SD).

4.7 Registry

Following first randomisation, 578 were withdrawn from the main study and the reasons for this are shown in Figure 26. These patients all received a single dose of prednisolone 40 mg prior to coronary angiography. Follow up data were not available for the patients recruited in Edinburgh due to funding and resource limitations. Of the 405 patients in the Middlesbrough cohort, the majority (72%) of patients did not receive a BMS because their coronary anatomy was such that for most of these patients either PCI with DES or CABG were preferable. In a minority of cases (n=20), revascularisation was not attractive because the lesions were in distal segments or small vessels and in three cases only PTCA was performed in vessels with small diameters. In 20 patients, follow on PCI was not performed because the lesions identified were not flow limiting as assessed by pressure wire studies or the vessels were occluded with no further symptoms and therefore revascularisation not indicated. A further 85 patients did not have an identifiable flow limiting or culprit lesion and therefore revascularisation was also not indicated. Of the 7 patients that did receive BMSs, in 2 there was no suitably sized study stent, 2 withdrew consent and in 3 the operator decided to use an alternative non study stent.

The mean age of the participants was 59.8 years (range 30-84 years), 83% were male, 11% were diabetic, 56% had a positive family of ischaemic heart disease, 51% had a history of hypertension, 89% had hypercholesterolaemia and 65% had a history of smoking. This was in keeping with the patients who

participated in the main trial (section 4.1). There was a smaller proportion of patients that had elective PCI (21%) compared to the main trial (42%).

Baseline characteristics are shown in Table 25. There were no significant differences between the group that received placebo and those who received prednisolone. In comparison to the main study, mean admission CRP was higher: 9.29 ± 17.0 mg/l compared to 6.65 ± 13.47 mg/l. The proportion of patients with a raised CRP (>5mg/l) was also higher, 40% compared to 29%.

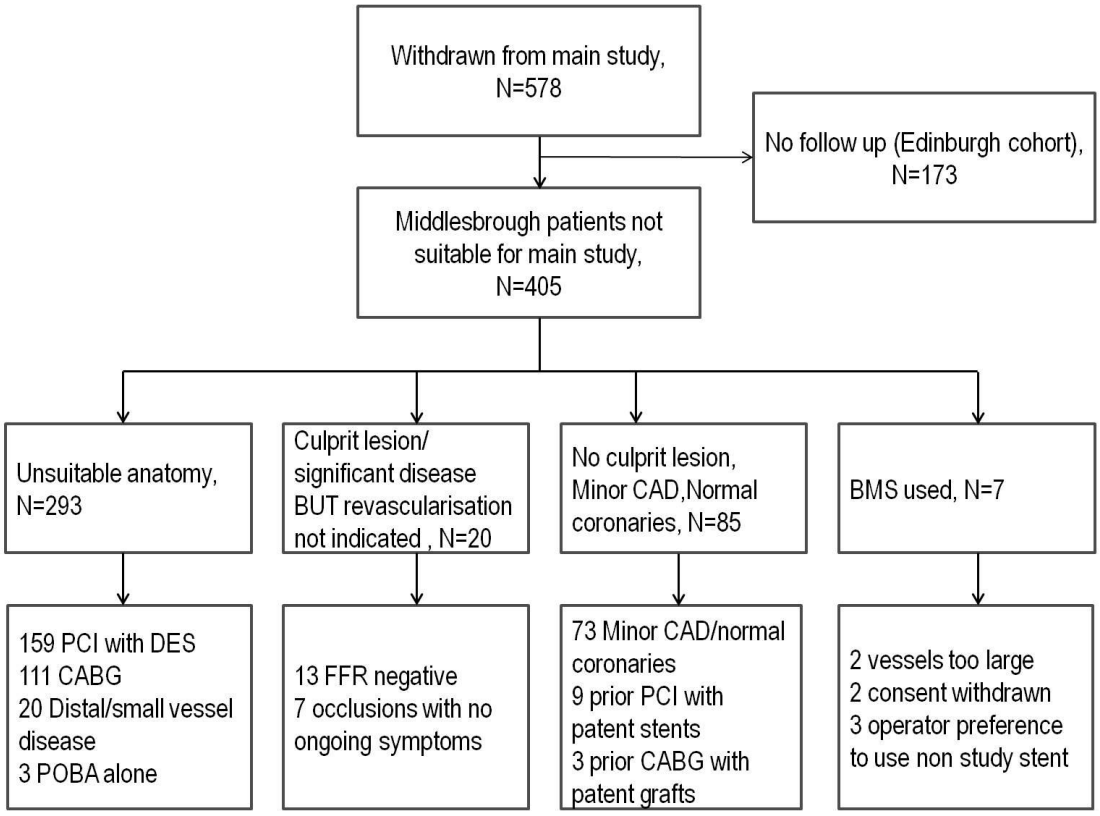


Figure 26. Consort diagram indicating the reasons bare metal stents were not used. PCI = percutaneous coronary intervention, CABG = coronary artery bypass grafting, POBA = plain old balloon angioplasty, FFR = fractional flow reserve, CAD = coronary artery disease.

	Placebo, N=213		Prednisolone, N=192		p
Male	176	(82.6%)	160	(83.3%)	0.90
Age, y	60.6	(9.13)	58.9	(10.5)	0.08
Height, m	1.73	(0.09)	1.73	(0.09)	0.87
Weight, kg	87.1	(16.4)	87.6	(19.1)	0.78
Smoking status					0.54
never smoked	77	(36.2%)	61	(31.8%)	
ex-smoker	80	(37.6%)	72	(37.5%)	
current smoker	56	(26.3%)	59	(30.7%)	
History of hypertension	109	(51.2%)	95	(49.5%)	0.77
Family history of IHD	130	(61.0%)	105	(54.7%)	0.23
Previous MI	34	(16.0%)	37	(19.3%)	0.43
Previous CABG	6	(2.8%)	5	(2.6%)	1.00
Previous PCI	24	(11.3%)	27	(14.1%)	0.45
History of CVD					0.51
TIA	6	(2.8%)	2	(1.0%)	
CVA	4	(1.9%)	3	(1.6%)	
History of PVD	2	(0.9%)	7	(3.6%)	0.09
History of LVSD	13	(6.1%)	11	(5.7%)	1.00
Renal disease	0	(0.0%)	1	(0.5%)	0.48
Diabetes (I or II)	25	(11.7%)	19	(9.9%)	0.63
Hypercholesterolaemia	185	(86.9)%	166	(86.5%)	1.00
Cholesterol, mmol/L	4.96	(1.25)	4.91	(1.38)	0.71
Creatinine value, µmol/L	93.0	(21.3)	92.8	(18.3)	0.90
Troponin, µg/L	1.69	(5.51)	1.27	(3.22)	0.43
Admission hs-CRP	9.43	(16.0)	9.14	(18.1)	0.87
HbA1C	5.45	(1.77)	5.65	(1.42)	0.27
Elective PCI	42	(19.7%)	43	(22.4%)	0.54
ACS type					0.41
Unstable angina	47	(22.1%)	33	(17.2%)	
Non-STEMI	113	(53.1%)	110	(57.3%)	
STEMI	11	(5.2%)	6	(3.1%)	
GPIIb/IIIa type					0.71
none	174	(81.7%)	154	(80.2%)	
Abciximab	39	(18.3%)	38	(19.8%)	
Tirofiban	0	(0.0%)	0	(0.0%)	
Aspirin	211	(99.1%)	186	(96.9%)	0.71
Clopidogrel	184	(86.4%)	168	(87.5%)	0.77
Beta blocker	184	(86.4%)	171	(89.1%)	0.69
ACE inhibitor	152	(71.4%)	149	(77.6%)	0.17
Statin	198	(93.0%)	178	(92.7%)	1.00

Table 25. Count data shown as: count (%); comparisons: Fisher's exact test. Numeric data shown as: mean (SD); comparisons: independent samples t-test.

IHD = Ischaemic heart disease, MI = Myocardial infarction, CABG = Coronary artery bypass grafting, PCI = Percutaneous coronary intervention, CVD= cerebrovascular disease, TIA = Transient Ischaemic attack, CVA = Cerebrovascular accident, PVD = Peripheral vascular disease, LVSD = Left ventricular systolic dysfunction, ACS = Acute coronary syndrome, GP IIb/IIIa = Glycoprotein IIb/IIIa inhibitor.

The angiographic findings, management strategies and final diagnoses are shown in Table 26. The two groups were well matched. In terms of management strategies after angiography, approximately 30% of patients were not revascularised. Amongst this group, 35 patients (8.6% of all patients), did not have a cardiac cause for their symptoms. They did not have any major adverse cardiovascular events within the 6 month follow up period.

4.7.1 Outcomes

There was no difference in any of the clinical endpoints between the two groups (Table 27). Of the seven patients who died:

- Five had inpatient CABG.
- Three of these patients died within the same hospital admission. Post mortems were held in two of these cases and the cause of death was pneumonia. In the third case, the patient fell sustaining a neck of femur fracture during the post-operative phase. The patient subsequently had a cardiac arrest during induction of anaesthesia and resuscitation was unsuccessful.
- In the two other cases, one patient died two months after study entry and no post mortem held but cause of death was certified as Ischaemic Heart Disease, and the other died four months into the study and the cause of death after postmortem was epicardial fibrosis.
- Of the patients who died and had not had CABG, one died of myocardial infarction. The patient had an elective angiogram having presented to the rapid access chest pain clinic with recent onset angina, was found to have severe three vessel disease and referred for

CABG. Post angiography, the patient had massive gastrointestinal bleeding caused by a duodenal ulcer which was controlled endoscopically but then had a STEMI with successful PPCI. This was complicated by stent thrombosis and despite prompt reperfusion, the patient went on to develop multi-organ failure and failed to recover. The other patient died of non cardiac causes, metastatic lung cancer.

Nine patients had myocardial infarction after entry into the study:

- One with STEMI as described above and the others had non ST elevation MI.
- Only two of these had repeat revascularisation, one in which a patient had thrombus aspiration following the index event and as the artery was ectatic with no flow limiting lesion, no stents were implanted. Repeat angiography during the same admission after a period of intravenous GpIIb/IIIa inhibitor therapy was unchanged. The patient was then readmitted one week later with further MI and had PPCI with stent implantation. In the other case, a patient with three vessel coronary artery disease was referred for CABG after presenting with an ACS but became unstable whilst waiting for this, had new ECG changes and further troponin rise and went on to have PCI with DES instead. This patient represented with unstable angina and angiography revealed significant ISR and therefore had repeat revascularisation.
- One had an early saphenous vein graft occlusion managed medically.
- One was felt to have coronary spasm.

- Another patient also had a STEMI whilst waiting for CABG and therefore had PCI with DES instead.
- One was admitted 2 days post PCI with further chest pain and an increase in troponin and repeat angiography revealed a small occluded side branch that was managed medically.
- Two presented to their local hospitals with ACS and were not referred for angiography.

Of the other 2 patients who had repeat revascularisation:

- One had ongoing angina with known residual coronary artery disease and therefore had further PCI to the non-target lesion.
- The other patient had recurrent angina with target lesion revascularisation for ISR within a DES.

The stroke occurred in a patient post CABG.

	Placebo, N=213		Prednisolone, N=192		p
Angiographic findings					0.13
1 VD	48	(22.5%)	58	(30.2%)	
2 VD with proximal LAD	21	(9.9%)	17	(8.9%)	
2 VD other	24	(11.3%)	27	(14.1%)	
3 VD	61	(28.6%)	41	(21.4%)	
LMS	13	(6.1%)	10	(5.2%)	
Management after angiography					0.94
PCI	88	(41.3%)	82	(42.7%)	
CABG	60	(28.2%)	51	(26.6%)	
No revascularisation	65	(30.5%)	59	(30.7%)	
Reason BMS not used					0.94
Unsuitable anatomy	155	(72.8%)	138	(71.9%)	
No culprit lesion	44	(20.7%)	41	(21.4%)	
No indication for revascularisation	10	(4.7%)	10	(5.2%)	
BMS used	4	(1.9%)	3	(1.6%)	
Diagnosis					0.96
Stable angina	34	(16.0%)	33	(17.2%)	
Unstable angina	33	(15.5%)	27	(14.1%)	
Non-STEMI	110	(51.6%)	102	(53.1%)	
STEMI	11	(5.2%)	6	(3.1%)	
Arrhythmia	4	(1.9%)	3	(1.6%)	
Other cardiac cause	3	(1.4%)	4	(2.1%)	
Non cardiac cause	18	(8.5%)	17	(8.9%)	

Table 26. Angiographic findings, management and final diagnosis. VD = vessel disease.

	Placebo, N=213		Prednisolone, N=192		p
MACCE	11	(5.2%)	7	(3.6%)	0.48
Death	3	(1.4%)	4	(2.1%)	0.71
Repeat MI	7	(3.3%)	2	(1.0%)	0.18
CVA	1	(0.5%)	0	(0.0%)	1.00
Repeat revascularisation	3	(1.4%)	1	(0.5%)	0.63
Repeat hospitalisation	17	(8.0%)	20	(10.4%)	0.94
Recurrent angina	12	(5.6%)	7	(3.6%)	

Table 27. Clinical endpoints. Count data shown as: count (%); comparisons: group %, Fisher's exact test. MACCE, major adverse cardiovascular and cerebrovascular events.

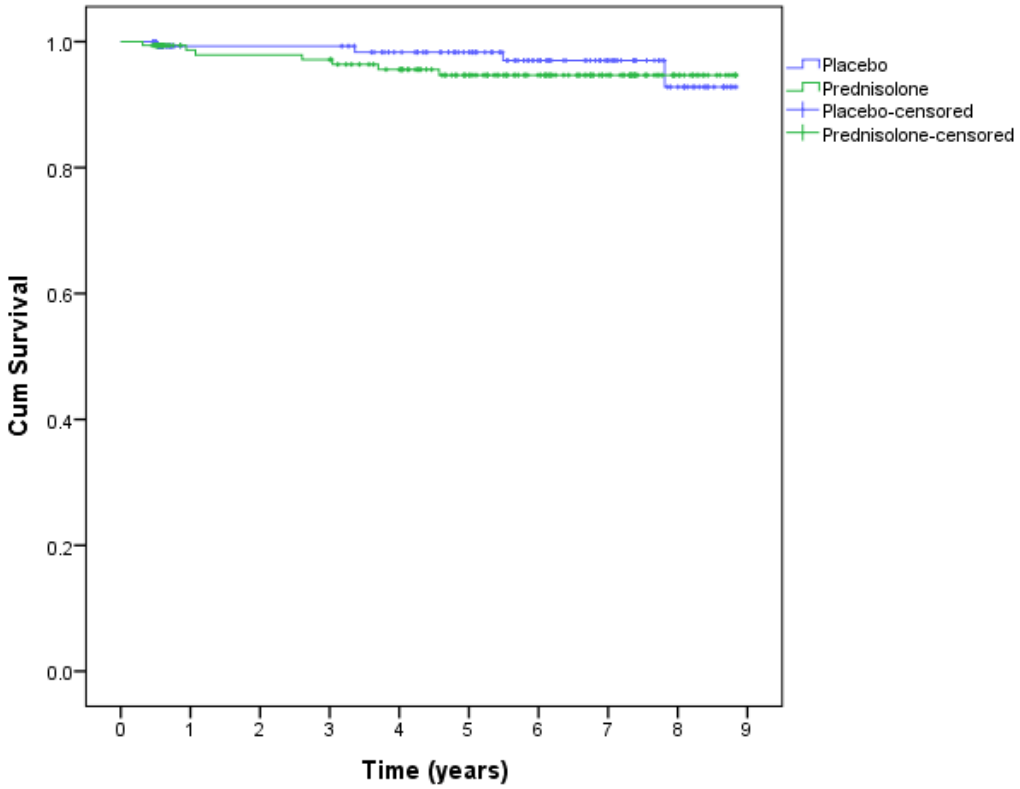
4.8 Longer term follow up

Patient recruitment took longer than anticipated and hence provided an opportunity for longer term follow up for clinical endpoints including death, target vessel revascularisation and repeat revascularisation. These data were collected by linking the hospital identification numbers with other databases that tracked mortality and in the case of repeat revascularisation, the British Cardiovascular Intervention Society dataset. This follow up could only be extended to the patients recruited at the James Cook University Hospital (n=242) due to resource limitations. Mean follow up was 1772 days (range 115-3226 days).

4.7.1 Placebo versus Prednisolone

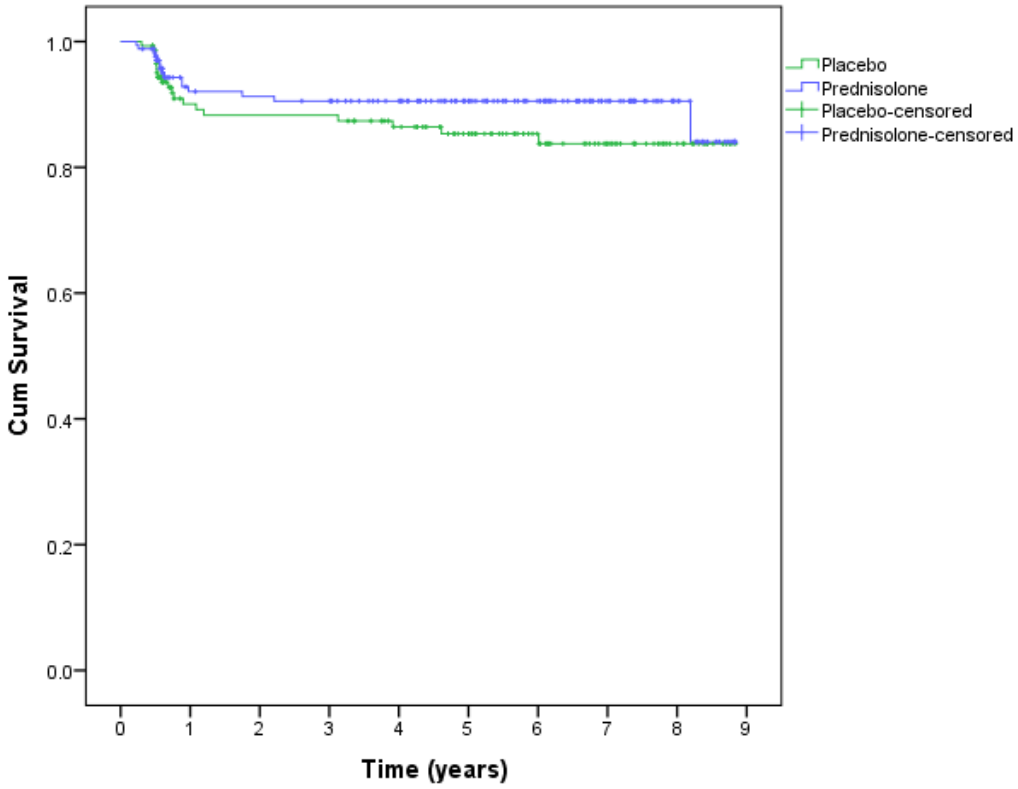
With regards to death, there was no difference between placebo and prednisolone, four deaths compared to seven, log rank p=0.50 (Figure 27).

There was no difference in TVR, 19 events vs. 15 for prednisolone, log rank p=0.24 (Figure 28). There was additionally no difference in any repeat revascularisation between the groups, 22 events vs. 24 for prednisolone, log rank p = 0.82 (Figure 29).



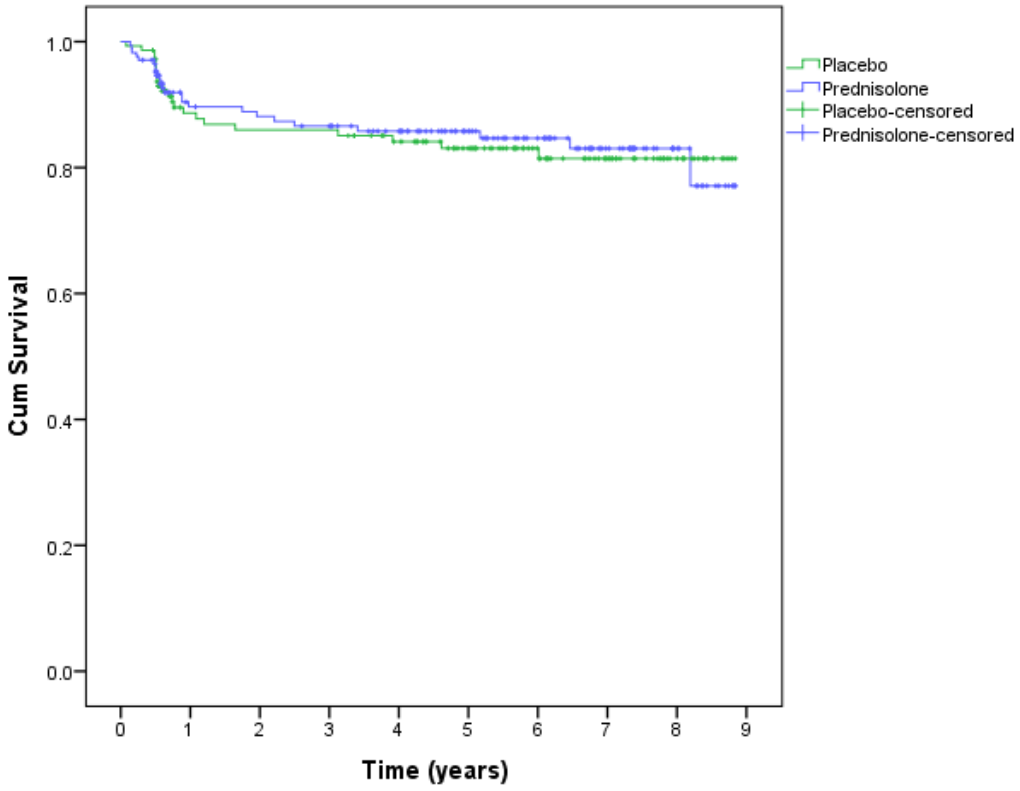
Placebo									
n	145	109	109	109	99	85	60	41	20
events	1	0	0	1	0	1	0	1	0
Prednisolone									
n	170	131	130	129	118	95	73	47	19
events	2	1	1	2	1	0	0	0	0

Figure 277. Kaplan-Meier event free cumulative survival comparing mortality between patients treated with prednisolone and placebo.



Placebo									
n	145	101	99	99	89	74	53	36	18
events	13	2	0	2	1	0	1	0	0
Prednisolone									
n	170	122	120	118	107	86	67	41	17
events	12	1	1	0	0	0	0	0	1

Figure 288. Kaplan-Meier event free cumulative survival comparing target lesion revascularisation between patients treated with prednisolone and placebo.



Placebo									
n	145	99	96	96	87	73	52	35	18
events	15	3	0	2	1	0	1	0	0
Prednisolone									
n	170	118	115	112	102	81	61	38	17
events	16	2	2	1	0	1	1	0	1

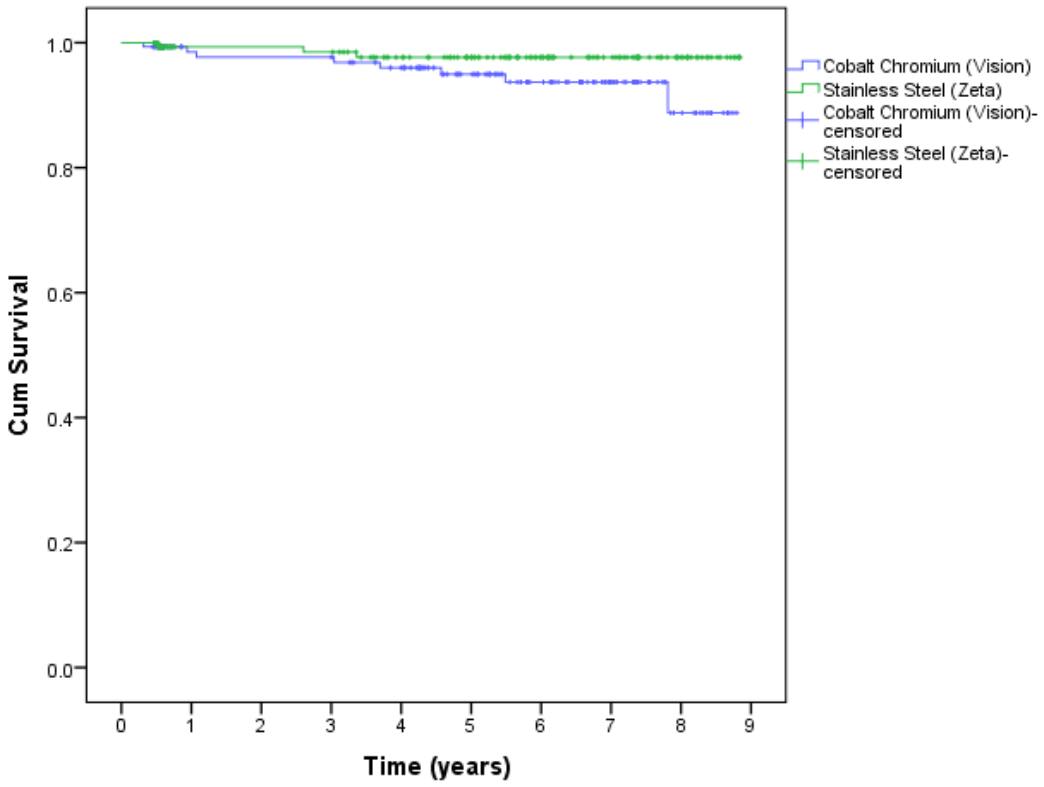
Figure 29. Kaplan-Meier event free cumulative survival comparing any repeat revascularisation between patients treated with prednisolone and placebo.

4.7.2 Cobalt Chromium versus Stainless steel

There was no difference between the stents in death, eight vs. three for stainless steel, log rank p=0.11 (Figure 30).

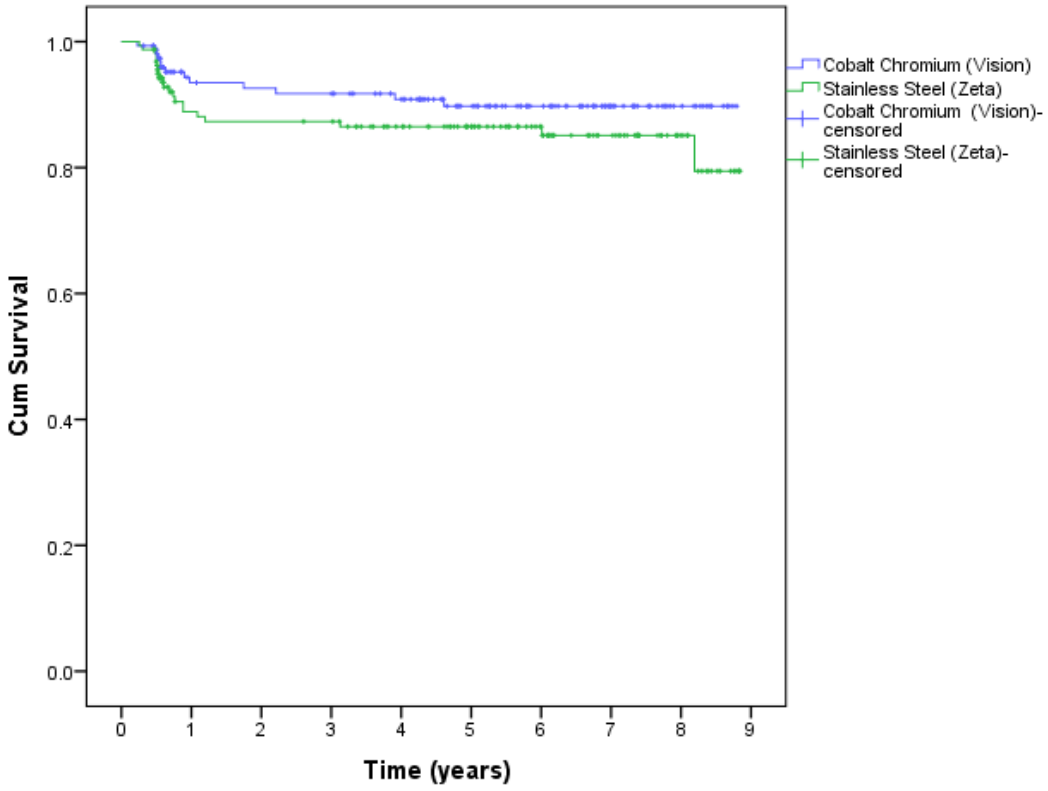
There was also no difference in target vessel revascularisation, 13 vs. 21 events for stainless steel, log rank p=0.19 (Figure 31).

There was also no difference in any repeat revascularisation, 21 vs. 25 events for stainless steel, log rank p=0.66 (Figure 32).



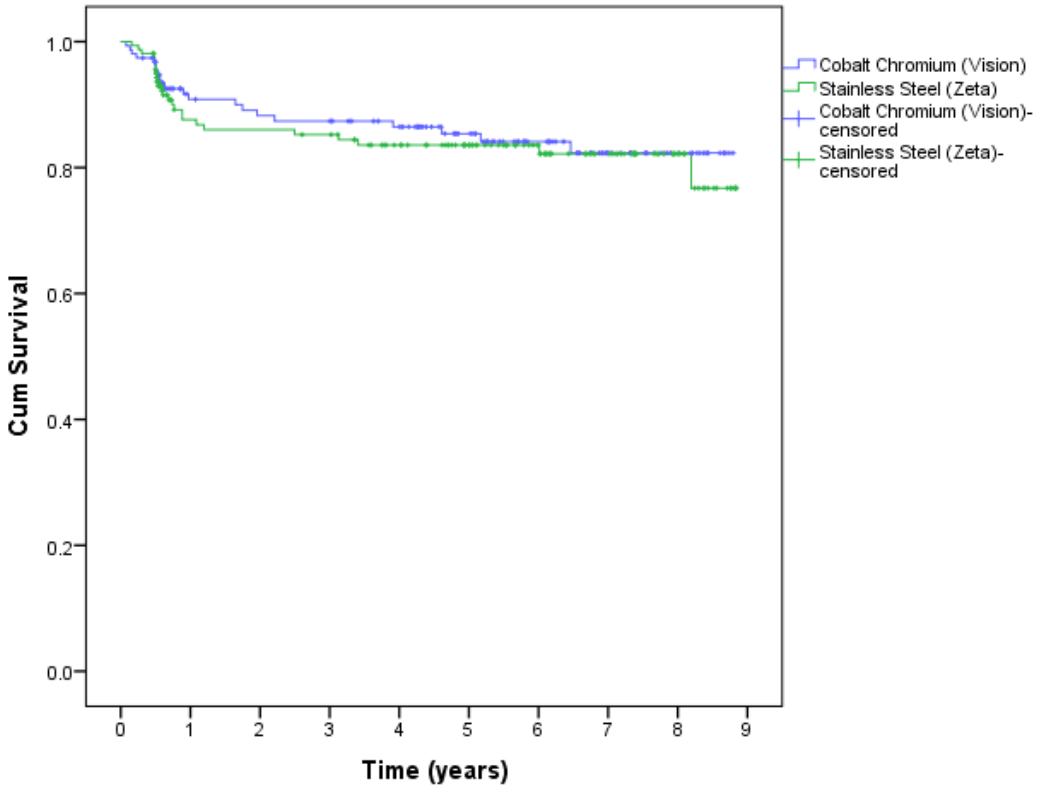
Cobalt Chromium									
n	155	118	117	117	110	87	66	40	16
events	2	1	0	2	1	1	0	1	0
Stainless Steel									
n	160	122	122	121	107	93	67	48	23
events	1	0	1	1	0	0	0	0	0

Figure 29. Kaplan-Meier event free cumulative survival comparing mortality between patients treated with cobalt chromium and stainless steel stents.



Cobalt Chromium									
n	155	110	108	107	99	77	58	34	15
events	9	1	1	1	1	0	0	0	0
Stainless Steel									
n	160	113	111	110	97	83	62	43	20
events	16	2	0	1	0	0	1	0	1

Figure 30. Kaplan-Meier event free cumulative survival comparing target lesion revascularisation between patients treated with cobalt chromium and stainless steel stents.



Cobalt Chromium									
N	155	106	102	101	94	73	53	31	15
events	13	3	1	1	1	1	1	0	0
Stainless Steel									
N	160	111	109	107	95	81	60	42	20
events	18	2	1	2	0	0	1	0	1

Figure 31. Kaplan-Meier event free cumulative survival comparing any repeat revascularisation between patients treated with cobalt chromium and stainless steel stents.

CHAPTER 5

Discussion

This trial was designed to address two separate questions. The first was whether there was any benefit of systemic corticosteroid therapy in preventing binary angiographic restenosis and the second was whether there was any impact upon on this outcome of introducing cobalt alloys in BMS. At the time it was conceived, both of these were seen as promising avenues to reduce restenosis rates particularly as there was concern about long term safety regarding DES with regards to stent thrombosis, particularly with first generation DES (73). The findings provide no support for improved outcomes from the use of 28-day prednisolone started at least six hours pre-procedurally or from the use of cobalt chromium stents. This was apparent in the primary outcome of binary angiographic restenosis and consistent in secondary outcomes.

5.1 The impact of glucocorticoids

The key studies investigating the role of glucocorticoids and their main findings prior to this study were reviewed in section 1.7.4. They included two randomised studies of balloon angioplasty alone by Stone et al. (n=105, 53% had repeat coronary angiography) and the M-HEART group of investigators (n=915, 74% had repeat angiography) respectively (122, 123). As discussed previously, there was no benefit of glucocorticoids in preventing restenosis in these groups. The lack of efficacy could be explained by the additional mechanism of elastic recoil and arterial remodelling following angioplasty alone which steroids might have no effect on.

Additionally, there were two randomised studies involving BMS implantation These included a study by Lee et al. (124) and the IMPRESS study (125). In

comparison to SSTARS, for the Lee et al. study (n=140, 91% had repeat angiography), only a single pulsed dose of intravenous methylprednisolone was used prior to the procedure and complex lesions were excluded but the results were similar.

With regards to IMPRESS, only a highly select group of patients were included (n=83, 98% had repeat angiography). These were patients with evidence of a persistent inflammatory response defined as those patients with normal CRP levels prior to their procedure with subsequently elevated levels (>0.5mg/dl) at 72 hours. Prednisone (reducing regimen of 1mg/kg for the first 10 days, 0.5 mg/kg from day 11 to day 30 and 0.25mg/kg from day 31 to 45) was administered 72 hours post procedure for 45 days and was associated with a quite marked reduction in restenosis; three patients (7%) in the prednisone arm had binary angiographic restenosis compared to 14 (33%) in the placebo group, $p<0.01$.

There were only a small proportion of patients in this study who would have met the IMPRESS inclusion criteria (n=28) albeit CRP was measured at day seven as opposed to day three. This was a key difference and notably there was no association between reducing CRP and lowering restenosis. This was demonstrated in the prednisolone treated group where although CRP was lowered significantly when compared to placebo, the rates of restenosis were similar.

Overall, from this cohort of non-selected patients, only a minority of patients fulfil the requirements of the IMPRESS protocol. Moreover, in routine clinical practice, the choice of stent at the time of the procedure i.e. BMS or DES

cannot be determined by what the hs-CRP might be a few days later. The logistics of arranging for a routine hs-CRP measurement at 72 hours and then determining the use of steroids is difficult for centres offering a regional service with early discharge as the standard protocol.

The results of the SSTARS study also differs from the Cortisone plus BMS or DES alone to Eliminate Restenosis (CEREA-DES) trial (n=375) (202). In this Italian multicenter trial, from the same group of investigators as IMPRESS, the study endpoint was not angiographic restenosis but rather a combined clinical endpoint of major adverse cardiovascular events (MACE) which was defined as cardiac death, myocardial infarction or repeat revascularisation (target vessel only). Participants were randomised into any of three arms, treatment with BMS alone, prednisone and BMS, and DES alone. The BMS plus prednisone group and DES groups were compared with the designated control arm (BMS alone). The IMPRESS steroid regimen was used but prednisone was commenced within the 48 hours after PCI rather than 72 hours post procedure as in IMPRESS.

Based on Kaplan-Meier survival analysis, there was a significant reduction of the primary endpoint in the prednisone plus BMS arm compared to BMS alone, event free survival 88.0% vs. 80.8% (hazard ratio [HR] = 0.51; 95% CI, 0.20 to 0.76; p = 0.006). The comparison between DES alone and BMS alone yielded similar results, event free survival 88.8% vs. 80.8% (HR = 0.46; 95% CI, 0.23 to 0.84; p = 0.004).

It is worth noting that there were no statistically significant differences in the individual components of MACE. In particular, clinical restenosis (TLR)

occurred in 15 out of 125 patients for BMS alone (12%) vs. 10 out of 125 (8%) for BMS plus oral prednisone, p=0.23. As with IMPRESS, diabetic patients were not included in this study but this was a more inclusive study with no prerequisite for elevated CRP levels. There was, however, a separate analysis performed in 61 patients in whom CRP was raised post PCI and there was a significant reduction in MACE (23% for BMS alone vs. 8% for prednisone plus BMS, p=0.03) but it is not clear whether this was driven by a need for less TLR. Another limitation of this trial was that there was no blinding of treatment in this study and in conjunction with mandated exercise stress testing at 6 months, this could have had a potential confounding influence on repeat revascularisation. In the DES group, for example, TLR was only 3.2% at one year but TVR was higher than would be expected at 11.2%.

The five randomised studies mentioned above were all included in the only meta-analysis investigating the role of corticosteroids in reducing restenosis rates in BMS (203). Separate analyses were performed for the two trials involving balloon angioplasty alone (122, 123) and three involving BMS implantation (124, 125, 202). In keeping with the individual trial data, there was no benefit of corticosteroids in preventing restenosis in the angioplasty alone group (RR 1.02, 95% CI 0.84-1.23, p=0.85). But corticosteroids did reduce restenosis following BMS implantation (RR 0.60, 95% CI 0.37-0.97, p=0.04) driven mainly by the results of the IMPRESS and CEREA-DES trials. The results of CEREA-DES were included but there was no repeat angiography in this trial and the authors have used the hierarchal TLR in place of binary angiographic restenosis in their analysis. Overall, the number

of patients was small despite the inclusion of the CEREA-DES cohort (n=460) and there was substantial heterogeneity both methodologically (timing of steroid, dose of steroid, elevated CRP only in IMPRESS) and statistically (I^2 = 54%). These factors limit the applicability of this analysis to the wider population.

There is only one other randomised trial that has investigated the use of glucocorticoids in preventing restenosis in BMS from an Iranian group of investigators (204). This study was not included in the meta-analysis described above. In this double blind randomised study that also excluded diabetic patients,100 patients in each arm received either intramuscular placebo or 40mg methylprednisolone 48 hours prior to PCI and then again two weeks later. There was no significant difference in restenosis at 6 months 21% for methylprednisolone vs. 24% for placebo, p=NS.

Apart from IMPRESS and CEREA-DES, all the randomised steroid trials, including SSTARS, have not shown a benefit for glucocorticoids in BMS. One of the possible reasons for this has already been highlighted, the selective inclusion of patients with persistent inflammatory response after 72 hours (only 15% of consecutive patients) in the case of IMPRESS. Another difference is that both IMPRESS and CEREA-DES utilised a high dose steroid regimen (reducing regimen of 1mg/kg for the first 10 days, 0.5 mg/kg from day 11 to day 30 and 0.25mg/kg from day 31 to 45) whilst not including diabetic patients. This dose was substantially higher than that used in all of the other trials including SSTARS.

The inclusion of diabetics in SSTARS influenced the steroid regimen chosen. It was selected after discussion with the local endocrine team to represent an “anti-inflammatory” dose used in other areas of medicine. The regimen utilised a lower total dose of steroid including a lower maximum dose in the early phase of treatment but would be sufficiently high to achieve the beneficial anti-inflammatory action sought whilst minimising the risk of side effects.

However, it is noteworthy that the results of the case-control IMPRESS-LD study suggested that a higher dose intensity for a longer period of time was needed to impact on restenosis. The “low-dose” regimen in this small study itself included a high dose of 1mg/kg for the first 5 days of treatment started after PCI (205). This may partly explain the difference in findings between IMPRESS and CEREA-DES compared to SSTARS and all the other trials. In the Italian studies, prednisone was well tolerated but in SSTARS, with more patients, there was an increase in transient hyperglycaemia in patients on prednisolone, even amongst non-diabetics. Bearing in mind the proportion of diabetics in the study was small (11%), the potentially greater anti-inflammatory activity with higher doses of prednisolone may therefore come at the cost of increased adverse effects.

The safety and tolerability of a course of glucocorticoids were a concern given the additional requirement for DAPT. The issue of hyperglycaemia has already been mentioned but in this group of patients did not result in any clinically important changes in outcomes or management. The other major concern was bleeding and it is reassuring that there was no significant difference between the groups with regards to this and in particular, major bleeding did not occur in any of the patients on prednisolone.

The steroid regimen in SSTARS was also chosen to address the issues of both timing and duration of therapy. In the previous studies various regimens were used including parenteral pulsed therapy pre-procedure only, parenteral pulsed therapy pre-procedure ± short course of oral therapy/further pulses and longer courses of oral therapy commenced post procedure (122-125, 202, 204). In SSTARS, by administering the prednisolone prior to PCI, this would ensure that there were already therapeutic levels of anti-inflammatory activity from the steroid to cover the initial injury from stenting as well as the resultant inflammation. The subsequent course over 28 days would cover any persistent inflammation to cover the duration of neo-intimal formation in BMS. Despite this potentially all-encompassing regimen, there was no significant reduction in restenosis.

5.2 The impact of CRP

As discussed above, the success of glucocorticoids in preventing restenosis has largely been seen only in the IMPRESS study which highlighted the potential role of CRP in identifying those patients most at risk or most likely to benefit from glucocorticoid therapy. Other observational studies also addressed the role of CRP mainly in the context of raised pre-procedural levels with varying results although a meta-analysis seemed to suggest a role for identifying patients at risk of restenosis if CRP was raised (see section 1.8). Based on these observations, separate analyses based on CRP measurements were performed in the SSTARS study.

In SSTARS, elevated pre-procedural hs-CRP was not associated with higher rates of restenosis OR 0.68, 95%CI 0.33-1.40, p=0.29. Even after adjusting

for significant factors and known risk factors for restenosis, this remained non-significant, OR 0.56, 95%CI 0.26-1.22, p=0.14 (section 4.5.1). Different cut-offs have been used in preceding studies to define elevated CRP and despite applying this to the SSTARS dataset, no significant association between CRP levels pre-procedure and restenosis was seen. Further analysis of these subsets may help to explain the reasons for this. Hs-CRP levels between 1.0-2.99 mg/l, although not statistically significant, appear to have higher restenosis rates than the other groups. Whilst this is within the normal laboratory reference range, these values may represent a group of patients with a baseline inflammatory tendency not likely to be associated with any other process. Approximately 60% of the patients in SSTARS were acute admissions and therefore hospitalised patients who are exposed to greater inflammatory stimuli e.g. hospital acquired infections. CRP is very much an acute phase reactant and so will rise in response to other inflammatory stimuli and so much higher levels of baseline CRP values might have occurred in some patients in response to these unknown stimuli, which may have no bearing on whether they are more likely to have restenosis (206). It is of note that in the SSTARS study the patients with the highest levels of CRP at baseline had the least restenosis. This, of course, has to be interpreted cautiously in the context of the small numbers of patients when categorising the data this way. Another important factor may be the relatively high use of statin therapy which also has been shown to have some anti-inflammatory effect and this may in effect have "watered down" any reaction that might have occurred in association with an elevated CRP.

There was also no correlation between lowering CRP and reducing restenosis. Prednisolone reduced hs-CRP levels significantly but this had no impact on restenosis. The reasoning above may also apply to this observation because systemic therapy with prednisolone may also have been effective against non-PCI related inflammation. The timing of CRP measurement is also relevant here because post procedure levels were measured at 7 day follow up. As discussed in section 1.8, increases in CRP levels can be detected at 12- 48 hours and the plasma half life is 19 hours (207). In SSTARS, CRP was not checked within this time period. Also, asking patients to return so early after discharge was not practical given that for some, it would mean travelling significant distances. As a result, patients with raised CRP post PCI which could be attributed to the procedure, based on the temporal relationship to the procedure and kinetic profile of CRP, might have been missed. In the IMPRESS study, the investigators managed to recruit these patients but there were only 83 patients in the study and this represented 15% of consecutive patients at their institution. In SSTARS, with day seven CRP rather than day three measurements, only 28 patients out of 275 patients with available samples (10.2%) fulfilled the IMPRESS criteria.

5.3 The impact of stent alloy

Another important factor that this trial investigated was the comparison between stainless steel and cobalt alloy stents. The background to this is related to randomised studies assessing the thickness of stent struts (section 1.9.2.4). In the ISAR-STEREO trial, thinner strut stainless steel stents compared to thicker strut stent with a similar design had significantly less late

lumen loss and binary angiographic restenosis (15% vs. 26%, p=0.003) (173). Similarly the ISAR-STEREO 2 trial showed that thicker strut stainless steel stents with a different design resulted in more restenosis compared to thin strut stents (18% vs. 31%, p<0.001) (19). As discussed in section 1.9, strut thickness is one of many stent design issues that have been investigated with regards to restenosis. The influence of these other design factors were minimised by using stents of similar design (Multilink) but composed of the two different alloys.

In SSTARS, there was no significant reduction in restenosis rates in the thinner strut cobalt alloy stent. An obvious difference was that the difference in strut thickness between the stents was more marked in the earlier trials. In the ISAR-STEREO trials, the comparison was between 50µm and 140µm stents whereas in SSTARS, the cobalt chromium stents were 81µm thick compared to 90-125µm for the stainless steel stents (variable strut thickness system which is thicker in straight areas and less in areas where the stent needs to bend). It also may be that the expected reduction of restenosis due to reduced strut thickness with cobalt chromium might have been countered by some other unknown factor.

Only one other single centre randomised study from Brazil (n=187) has compared the influence of metal alloy (stainless steel vs. cobalt chromium) on restenosis and in keeping with SSTARS there was no difference in this outcome (208). The study design was, however, different from SSTARS in that both types of stents were implanted in the same patient. In the majority of patients, the stents were implanted into different vessels but in 30% of cases,

both stents were implanted into the same vessels where lesions were more than 10mm apart. Randomisation was to determine which stent was implanted first. There were also differences in baseline characteristics particularly a larger proportion of diabetics (36%) with resultant higher rates of restenosis (34% vs. 32%, SS vs. CoCr, p=0.80).

A number of different stainless steel stents were used in the trial and a separate three way analysis comparing the cobalt chromium stent used (60µm, Prokinetic™, Biotronik, Germany), thin strut stainless steel stents (<100µm) and thick strut stainless steel stents was also performed. The restenosis rates were 32.3%,33.2% and 35.1% respectively, p=0.89.

There is also scant experimental data on the subject. A small non-randomised animal study compared stainless steel stents (120µm strut thickness) and cobalt chromium stents (90µm strut thickness) implanted into normal porcine coronary arteries (n=9, 18 stents implanted, 7 CoCr, 11 SS). QCA and histopathological analysis was performed and there was no advantage of cobalt chromium compared to stainless steel with regards to late lumen loss and neointimal area from histopathological samples (209).

In SSTARS, there was a trend towards more target lesion revascularisation with the stainless steel stents compared to cobalt chromium (9.4% vs. 3.9% , p=0.07). The results on types of restenosis (section 4.3) may provide an explanation for this. Class III or IV restenosis (proliferative or occlusive respectively) occurred more often in the stainless steel group and higher TLR is known to occur with higher restenosis class (35). Of the six patients (7 lesions), the stented segment was >30mm in five lesions and they were all

treated with stainless steel stents. The reasons for this difference may therefore be to do with the types of lesion treated as opposed to the stent material. Other factors such as differences in the delivery system may also be a factor and the possibility of this being a chance finding cannot be excluded.

Being a 2x2 factorial design, the trial was not powered to detect a stent-drug interaction but nonetheless provided an interaction observation which was evident in the way binary angiographic restenosis was distributed. Within the stainless steel group, there is a numerical reduction in restenosis by prednisolone whereas the opposite occurs in the cobalt chromium group. The weight percentage of nickel and molybdenum is higher in 316L stainless steel than cobalt chromium (156) and the release of these metal ions may trigger local immune and inflammatory responses in susceptible individuals (177). Whilst this may provide a plausible basis for a stent-drug interaction, it is more likely that this observation is a chance finding and an artefact of dichotomising continuous data as it is only apparent in the restenosis data (section 4.2) for dichotomised thresholds around 40-50% and not apparent for higher or lower threshold values.

Whilst there was no advantage seen with the use of cobalt chromium stents over stainless steel stents there was also no disadvantage. Most of the discussion has focussed on strut thickness and because of the ISAR-STEREO trials this led to the assumption that thinner struts induce less injury and therefore there is less restenosis as a consequence. However, their own analysis showed that the advantage of thin strut stents was predominantly in the more complex lesions (B2 or C). In SSTARS, the majority of lesions were

not complex lesions because the availability of DES precluded their use in the most complex lesions whereas ISAR-STEREO was undertaken prior to the DES era with resultant higher rates of complex lesions treated. This may, in part, have contributed to the lack of success of the cobalt stents in SSTARS. Separate analysis of restenosis (using the averaged reference diameter) for complex lesions only did not reveal any significant difference between the stents either (25.5% for CoCr vs. 31.1% for SS, p=0.55) but this is limited by the small numbers of patients (n=122). The properties of cobalt chromium stents including better radiopacity and higher radial strength allows them to be more deliverable and better suited to treating more complex lesions in smaller, more tortuous arteries and with ostial lesions with elastic fibres. In current practice, DES are more likely to be employed in these types of lesions and it is therefore not surprising that these newer alloys have replaced stainless steel as the platform for DES. One of the key reasons for exploring other avenues to reduce restenosis in the DES era was the safety concerns especially with regards to DAPT duration but there have been further developments including the evolution of newer generation DES and optimal duration of DAPT (see section 6.0).

In conclusion, the SSTARS study showed that treating patients upstream with a moderately high dose of prednisolone to cover most of the period of inflammation associated with restenosis in BMS did not reduce the incidence of binary angiographic restenosis. In addition, there was no significant reduction in restenosis rates with stents composed of cobalt chromium alloy compared to stainless steel. There was also no difference in longer term clinical outcomes between the different arms of the study.

CHAPTER 6

Study Limitations

This study was designed as a superiority study to compare the effects of two interventions, oral prednisolone and cobalt chromium stents, in reducing the restenosis seen with stainless steel stents. This required two randomisations. Changing circumstances during the course of the study presented recruitment challenges, ultimately resulting in the recruitment target not being met. There was a change in the pattern of PCI delivery, with a shift towards more acute cases and an increasing use of ad hoc PCI (and so the angiographic features were not known when many patients were first approached and recruited). This, coupled with the progressive increase in DES use, resulted in failure of patients initially recruited to progress to the second randomisation. The increase in DES use was largely the result of the evidence base behind a National Institute of Health and Care Excellence (NICE) recommendation that DES should be used in arteries less than 3mm in diameter or lesions greater than 15mm in length (210). Patient concerns about prednisolone and side effects and the need for repeat coronary angiography were also factors. As a result we approached many patients with a smaller proportion being recruited than was anticipated. As time progressed, the number of patients who were eligible for the study (i.e. who were deemed to be preferentially treated with BMS) fell dramatically. We approached approximately four patients for every patient who consented to the first randomisation. Of those who consented, only about 1 in 3 were suitable for randomisation after angiography. The Steering Committee of the trial recommended its early termination when it became clear that the resources of the study were insufficient to extend the time needed or to set up new centres. However, given the small differences in

results observed, it is unlikely that a statistically significant difference in restenosis would have been achieved if the recruitment target had been met.

Another potential limitation is lack of operator blinding to stent type. This would not have been easy to achieve considering the different appearances of the stents used. However, the primary endpoint of binary angiographic restenosis was assessed without knowledge of stent type deployed. Hence we do not believe this is a major failing. There was no core laboratory analysis of the angiograms but analyses were performed by a single research fellow separate from the clinical team. Statistical analysis was performed independently from the clinical team.

CHAPTER 7

Safety concerns and the evolution of DES

In section 1.6 the initial evolution and concerns about DES were reviewed. The encouraging early results of first generation DES compared to BMS in terms of reduced restenosis and repeat revascularisation were dampened by the ESC firestorm controversy particularly with regards to the risk of stent thrombosis and perceived increased mortality. Some of these concerns were allayed at the time and multiple subsequent patient based meta-analyses found that first generation DES were safe when compared to BMS (71, 211-213). The controversy surrounding this issue led to renewed interest in the field and a knock-on effect of this was the development of second generation DES.

As has been alluded to already, stent thrombosis was the major safety concern with regards to DES but there were limitations in its definition which revolved around a 30 day limit. Within 30 days, acute or sub-acute stent thrombosis had occurred if there was angiographic vessel occlusion, any new Q-wave MI in an area supplied by the stented vessel, and/or unexplained death from a cardiac cause. Beyond 30 days, late stent thrombosis occurred only if there was angiographically confirmed new MI with occlusion of the stented artery, and, importantly, excluded patients who had previously undergone repeat TLR (214). Based on this definition, an increased incidence of late stent thrombosis was observed following first generation DES compared to BMS (211, 212, 215).

There were two main problems with this definition. Firstly, it underestimated the incidence of stent thrombosis since unexplained MI in the territory of the stented vessels and late deaths, which may have been due to stent

thrombosis, were usually not included. Secondly, there was potential for bias in favour of BMS because repeat TLR was more likely to occur in a patient with a BMS due to the more frequent need for repeat revascularisation.

New definitions were subsequently introduced by the Academic Research Consortium, a collaboration between academic research organisations in Europe and the United States (33). This definition includes three temporal categories with acute (<30 days), late (30 days to 1 year), and very late (>1 year) stent thrombosis. There are also three levels of evidence:

- Definite - which includes angiographic confirmation of a thrombus that originates in the stent or in the segment 5 mm proximal or distal to the stent, with or without vessel occlusion, which is associated with acute onset of ischaemic symptoms at rest or electrocardiogram (ECG) signs of acute ischemia or typical rise and fall of in cardiac biomarkers within 48 hours of angiography **OR** pathologic confirmation of stent thrombosis determined at autopsy or from tissue obtained following thrombectomy.
- Probable - which includes unexplained death occurring within 30 days after the index procedure, or an MI occurring at any time after the index procedure that was documented by ECG or imaging to occur in an area supplied by the stented vessel in the absence of angiographic confirmation of stent thrombosis or other culprit lesion.
- Possible - which includes unexplained death occurring more than 30 days after the index procedure.

Furthermore, the inclusion of all target lesion–related re-interventions was proposed. The combination of “definite” and “probable” has been recommended as the best way to characterize DES safety. Revisiting a pooled analysis using the ARC definitions resulted in an overall increase in rates of stent thrombosis (214) , with a nearly identical combined incidence in DES and BMS, and a trend toward more very late stent thrombosis with DES (213).

To recap, DES are usually composed of a metal stent platform and a polymer loaded onto this from which there is local delivery of the drug. Whilst stent thrombosis is a multifactorial entity where patient, lesion and procedural aspects can all be implicated, specific DES related issues such as delayed or incomplete endothelialisation and potential for hypersensitivity were targeted. This was particularly the case for first generation DES because of the non-bio-compatible polymers used where histopathological studies showed that they induced hypereosonophilia, localised vascular inflammation and apoptosis of smooth muscle cells all with potential for activating thrombosis (77, 216-219).

Both types of first generation DES, the Cypher sirolimus eluting stent (C-SES) and Taxus paclitaxel eluting stent (T-PES), had thick strut stainless steel platforms with non-bio-compatible polymers polyethylene co-vinyl acetate/poly-n-butyl methacrylate and polystyrene-b-isobutylene-b-styrene respectively. For C-SES, 80% of drug was released by 28 days and less than 10% for T-PES in the same time period. For the second generation DES, the aim was to improve all elements of the stent to minimise both the injury and healing phases of the artery. The second generation Endeavor ™ (Medtronic,

Minneapolis, Minnesota) zotarolimus eluting stent (E-ZES) and Xience V™ (Abbott Vascular, Santa Clara, California) everolimus eluting stent (X-EES) both employed thinner strut cobalt chromium stent platforms (Vision and Driver respectively). They also utilised thinner, more biocompatible polymers, phosphorylcholine for E-ZES and polyvinylidene fluoride co-hexafluoropropylene and poly-n-butyl methacrylate for X-EES. Both drugs were derivatives of sirolimus with similar mechanism of action (see section 1.6). The drug elution kinetics were also altered for E-ZES, 95% of the drug being released within 14 days in order to reduce delayed endothelialisation. For X-EES, as with C-SES, 80% of drug was released by 28 days (220).

The impact of these changes when compared to first generation DES was assessed in randomised trials. The Endeavour (Endeavor ABT-578-eluting phosphorylcholine-encapsulated stent system in de novo native coronary artery lesions) III trial compared E-ZES (n=436) with C-SES (n=113). In this relatively small single blinded trial in low risk patients with single vessel disease, somewhat predictably, E-ZES, with shorter release time of the drug, had higher late loss compared to C-SES (0.34±0.44 mm vs. 0.13±0.32 mm respectively; $p < 0.001$). In-segment binary angiographic restenosis was also higher in the E-ZES cohort (11.7% vs. 4.3%, $p = 0.04$) (221). Clinically-driven target lesion revascularization was also numerically higher for E-ZES at nine months (6.3 versus 3.5 percent, p=NS). Although not powered to assess this, the protocol specified five year follow up (95% complete) reported lower clinical endpoints for E-ZES including all-cause mortality (5.2% vs. 13.0%, $p = 0.02$), MI (1.0% vs. 4.6%, $p = 0.03$), and the composite event rates of cardiac death/MI (1.3% vs. 6.5%, $p = 0.009$) and major adverse cardiac events

(14.0% vs. 22.2%, p = 0.05) but no statistically significant difference in TLR (222). E-ZES (n=773) were also compared to T-PES (n=775) in the Endeavour IV trial. Once again, late loss was higher 0.67±0.49 mm compared to 0.42±0.50, p<0.001. In segment binary restenosis rates were 15.3% vs. 10.4%, p=0.28 in patients with angiographic follow up (n=144 for E-ZES and n=135 for T-PES). There was no statistically significant difference in the primary clinical end point of target vessel failure (TVF), defined as the composite of cardiac death, MI, or clinically driven target vessel revascularization (TVR) at 9 months after the procedure: 6.6% for E-ZES versus 7.1% for T-PES (223). At five years, the difference in TVF was not statistically significant (17.2 vs. 21.1 percent, respectively, p=0.06), but the rate of death or MI was lower with E-ZES (6.4 versus 9.1; p = 0.048) (224). In summary, E-ZES are inferior to SES and PES with respect to the angiographic finding of late loss. With respect to clinical outcomes, E-ZES has similar or better outcomes than PES but this is less clear when comparing ZES to SES. There appears to be similar or improved safety but with higher early rates of revascularisation with E-ZES.

X-EES were also subjected to randomised comparisons initially against T-PES. The SPIRIT (Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the treatment of patients with de novo native coronary artery lesions) II (X-EES, n=223; T-PES, n=77) and III (X-EES, n=669; T-PES, n=333) studies both showed superiority of X-EES in terms of late loss (0.11±0.27 mm vs. 0.36±0.39 mm, p<0.001 and 0.14±0.41mm vs. 0.28±0.48 mm, p <0.05 respectively) (225, 226). For the SPIRIT III cohort (92% follow up), at five years, X-EES had lower 5-year Kaplan-Meier rates of

TVF (death, MI, or ischemia-driven TVR), 19.3% vs. 24.5%, p = 0.05; TLF (cardiac death, target-vessel MI, or ischemia-driven TLR) 12.7% vs. 19.0%, p = 0.008; and MACE (cardiac death, MI, or ischemia-driven TLR) 13.2% vs. 20.7%, p = 0.007. X-EES also resulted in reduced rates of all-cause death (5.9% vs. 10.1%, p=0.02) (227). Additionally the SPIRIT IV (n=3687, 2:1 randomisation) and the COMPARE (Second-Generation Everolimus-Eluting and Paclitaxel-Eluting Stents in Real-Life Practice; n=1800, 1:1 randomisation) studies were the first to demonstrate a significant reduction in stent thrombosis between two DES. At 12-month follow-up, rates of definite/probable stent thrombosis for X-EES and T-PES were 0.17% vs. 0.85% (p = 0.004), and 0.7% versus 2.6% (p = 0.002) in the SPIRIT IV and COMPARE studies, respectively (228, 229). A meta-analysis including these trials (n=6792) also supported clinical superiority of X-EES compared to T-PES in terms of MI (OR 0.56, 95% CI 0.43-0.72), definite and probable stent thrombosis (OR 0.32, 95% CI 0.20-0.51) and ischaemia-driven TLR (OR 0.57, 95% CI 0.46-0.71). Importantly, for stent thrombosis, the reductions applied to early stent thrombosis (within 30 days) (0.2% versus 0.9%; OR: 0.24; p=0.0005), late (day 31-365 days) (0.2% versus 0.6%; OR: 0.32; p=0.01), and very late stent thrombosis (>365 days) (0.2% versus 0.8%; OR: 0.34; p=0.009). For death, the results were not statistically significant (OR 0.8, 95% CI 0.59-1.07) (230). In summary, these studies have shown superiority both in terms of efficacy and efficacy in favour of X-EES compared to T-PES.

When compared to C-SES, the results have been more comparable. The SORT OUT IV trial (Scandinavian Organization for Randomized Trials with Clinical Outcome) randomised patients between X-EES (n=1390) and C-SES

(n=1384). At nine month follow-up, the primary composite end point of cardiac death, MI, definite stent thrombosis and TVR occurred in 68 patients (4.9%) treated with the X-EES compared with 72 patients (5.2%) treated with C-SES (HR 0.94; 95% CI, 0.67-1.31). There was also no significant difference at 18 month follow-up (HR 0.94; 95% CI, 0.71-1.23). With regards to definite stent thrombosis, the results favoured X-EES. At nine months, this occurred in two patients (0.1%) treated with X-EES versus nine (0.7%) in the C-SES group patients (hazard ratio, 0.22; 95% confidence interval, 0.05-1.02) and at 18 months this difference was sustained (3 patients [0.2%] vs. 12 patients [0.9%]; HR 0.25; 95% CI, 0.07-0.88) (231). At three year follow up, there was also no significant difference in a composite outcome of all death, all MI, or any revascularisation or a stent-related composite outcome of cardiac death, target vessel MI, or symptom-driven TLR. The rate of definite stent thrombosis was however lower for X-EES (0.2 versus 1.4 percent; hazard ratio 0.15, 95% CI 0.04-0.50) (232). A meta-analysis of five randomized trials (n= 7370 patients with no significant heterogeneity), including SORT OUT IV, found no significant difference in the rate of the major composite end point (HR 0.91, 95% CI, 0.77-1.08,p=0.28) or in any of the components (cardiac death, MI, repeat revascularisation, and the composite of definite and probable stent thrombosis) at a median follow-up of 13.3 months (233).

Key findings from the studies above are that the second generation DES have, at the very least, showed similar efficacy compared to first generation C-SES but also, particularly with X-EES, a more impressive safety profile particularly against T-PES. There was also a relatively high late lumen loss observed in the above studies of E-ZES. Given that the newer DES all

benefitted from improved stent platforms and polymers, it would therefore appear that drug choice and release kinetics are also important components of DES technology, especially as they relate to the vascular responses elicited by these devices.

Whilst both sirolimus (and its analogues everolimus and zotarolimus) and paclitaxel reduce restenosis by disrupting smooth muscle cell cycle progression, their mode of action differs, sirolimus being predominantly cystotatic compared to the more cytotoxic paclitaxel (see section 1.6). There are also data from animal studies on how sirolimus and paclitaxel are different in terms of their effects on the arterial wall. In a rabbit study of iliac artery stent implantation, oral everolimus has been shown to dose-dependently suppress neointimal formation. With high dose everolimus treatment, there was markedly reduced neointimal formation at the expense of delayed arterial healing, characterised by prolonged fibrin deposition and poor re-endothelialisation. Lower doses resulted in a similar benefit in terms of neointimal inhibition but signs of delayed arterial healing were absent, suggesting a wide therapeutic index of everolimus (234). The cytotoxic properties of paclitaxel on porcine arteries, on the other hand, have been reported with increased medial wall necrosis, smooth muscle cell loss, and arterial dilation with increasing doses in paclitaxel-coated Palmaz-Schatz stents (235). This coupled with the slower release profile of paclitaxel from T-PES already mentioned may explain the main differences between X-EES and T-PES.

One study that deserves separate mention is the PROTECT trial (Patient Related OuTcomes with Endeavour vs. Cypher Stenting Trial). This was the

largest head to head DES study and only study powered to detect a difference in rates of definite or probable stent thrombosis. Participants were randomised to E-ZES (n=4357) or C-SES (n=4352) based on the premise that they have different anti-proliferative properties and thus different vascular healing responses. After three years (98% follow up), there was a non-significant difference in the primary endpoint of definite or probable stent thrombosis (1.4% for E-ZES vs. 1.8% for C-SES, p=0.17) with higher rates of TVR with E-ZES (236). At pre-specified longer term follow up of 4 years (98% follow up) and 5 years (96% follow up) this difference was now significant (1.6% for E-ZES vs. 2.5% for C-SES, p=0.003 and 1.7% for E-ZES vs. 2.8% for C-SES, p<0.001 respectively) (237, 238). There was also a reduction in the composite secondary endpoint of death/MI (8.2% for E-ZES vs. 9.6% for C-SES, p=0.02). Dual antiplatelet therapy was used in 96% of patients at discharge, 88% at 1 year, 37% at 2 years, 30% at 3 years, 27% at 4 years and 26% at 5 years. This highlighted the importance of longer term follow up in these types of studies particularly as the higher incidence of these events occurred very late when DAPT use decreased.

The mechanisms of very late thrombosis with regards to DES warrant further mention. These include stent malapposition, particularly late acquired stent malapposition. This is thought to be caused by positive vascular remodelling which occurs when the vessel pulls away from the stent. More commonly seen in first generation DES and rarely with BMS, it therefore probably represents a local effect of the drug or the polymer. Inflammatory changes and hypersensitivity reactions in the intima and media with vasculitis, apoptosis, eosinophil and lymphocyte infiltration, and necrosis have been

seen in autopsy studies of stent thrombosis. Chronic inflammation of this type is associated with local release of collagenases that weaken the vessel wall and lead to its expansion (239). Another prevailing mechanism that has been put forward is in-stent neo-atherosclerosis already discussed in section 1.6 and as mentioned there, it occurs earlier in first generation DES when compared to BMS. In essence, these mechanisms for very late stent thrombosis are a consequence of a local vascular response following stent deployment, particularly first generation DES. The results of the trials discussed above, seem to indicate that both X-EES and E-ZES with their changes in drug and delivery have had a beneficial impact. Stent thrombosis has remained an issue in the second generation DES era but like with BMS, it has been accepted that this complication of PCI will occur, but fortunately, relatively infrequently.

In the BMS era, the advent of DAPT, particularly the addition of P2Y12 inhibitors such as clopidogrel, heralded improvements in outcomes after PCI but it was standard practice to only use combination therapy for one month. Because of the stent thrombosis concerns with first generation DES, most authorities recommended 12 month duration of DAPT and this was a reason for exploring other avenues to reduce restenosis (as with SSTARS). With the new found confidence in second generation DES with less inflammatory polymers amongst other changes, the case could now be made for a shorter duration of DAPT but at the same time, the mechanisms of very late stent thrombosis were becoming apparent and given that these issues may still apply in second and third generation DES, there has been continuing

uncertainty about the optimal duration of DAPT. A number of trials have investigated this further.

7.1 Duration of anti-platelet therapy after stenting

The safety of using shorter duration of DAPT with second generation DES has been investigated using both E-ZES and X-EES in a series of relatively small randomised non-inferiority trials with short to medium term follow up:

- In the EXCELLENT (Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting) trial, patients were randomised to six (n=722) versus 12 (n=721) months of DAPT after implantation of first (C-SES, n=364) and second generation (X-EES, n=1079) DES. The primary outcome of target-vessel failure (cardiac death, MI, or ischaemia-driven TVR) was similar (4.8% vs. 4.3% for 12 month DAPT, p=NS) and in addition, landmark analysis at 6 months showed comparable event rates with six versus 12 months of DAPT (hazard ratio, 1.06; 95% CI, 0.56–2.03; *P*=0.85) (240). Approximately 50% of patients had presented with an ACS.
- In the PRODIGY (Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intima Hyperplasia Study), patients were first randomized to receive BMS (n=492) versus E-ZES (n=493) versus T-PES (n= 490) versus X-EES (n=495) and 30 days after the procedure underwent a second randomization for allocation to six versus 24 months of DAPT. The majority of patients included had presented with an ACS (75%). At 24 months, the primary outcome (death from any cause, MI, or stroke) was similar, 10.1% in the 24-month DAPT group

compared with 10.0% in the six month DAPT group (HR, 0.98; 95% CI, 0.74–1.29) (241). There was also no difference in the cumulative rates of definite or probable late or very late stent thrombosis (1.3% vs. 1.5%, p=0.70). With regards to bleeding, in patients assigned to receive 24 month DAPT, there was a roughly 2-fold greater risk of clinically important bleeding (HR 2.17; 95% CI, from 1.44–3.22; *P*=0.00018) (241) according to the Bleeding Academic Research Consortium classification (types 2-5) (242). A subsequent pre-specified post hoc analysis from PRODIGY with landmark analysis at 6 months showed lack of benefit for prolonged DAPT with BMS and second generation DES (E-ZES and X-EES). Patients treated solely with paclitaxel-eluting stents did, however, benefit from prolonged dual antiplatelet therapy (243).

- In the RESET (Real Safety and Efficacy of 3-Month Dual Antiplatelet Therapy Following Endeavor Zotarolimus-Eluting Stent Implantation) trial, 2117 patients were randomized to treatment with E-ZES plus three months of dual antiplatelet therapy compared to first or second generation DES plus 12 months of DAPT. For the 12 month group, multiple stents were used depending on lesion length. Approximately half of the patients were recruited following an ACS. Patients with short lesions (≤ 24mm) received E-ZES or C-SES and those with long lesions received E-ZES or X-EES. At 12 months' follow-up, the primary outcome (cardiac death, MI, stent thrombosis, or ischemia-driven target-vessel revascularization) was equal in both groups, 4.0% for three months therapy compared to 4.7% for 12 months therapy (95%

CI -2.5 to 2.5%). The rates of stent thrombosis were also similar (0.2% for three months therapy versus 0.3% for 12 months therapy, 95% CI: −0.5 to 0.3) (244).

- In the OPTIMIZE (Optimized duration of clopidogrel therapy following treatment with the Endeavor zotarolimus-eluting stent in real-world clinical practice) trial 1563 patients were randomised to three month DAPT versus 1556 patients randomised to 12 month DAPT (245). There was excellent compliance with DAPT and approximately 30% of patients were enrolled following recent ACS (NSTEMI 5%).There was no difference in the primary endpoint at one year of net adverse clinical and cerebral events (NACCE) which was a composite of death from any cause, MI, stroke, or major bleeding (6.0% vs. 5.8% for 12 month DAPT, 95% CI, −1.52 to 1.86). Definite or probable stent thrombosis rates were low and not different (0.6% vs.0.7% for 12 month DAPT (HR, 0.81 [95% CI, 0.34 to 1.96]) up to 90 days. Beyond 90 days, there was also no significant difference in these events (0.3% vs. 0.1% for 12 month DAPT groups, HR, 3.97 [95% CI, 0.44-35.49]) bearing in mind that the study was not powered to assess these.

These results suggested safety and efficacy of short-term DAPT in patients treated with second-generation drug-eluting stents but they are limited by their small sample sizes and low event rates. An attempt to address this with a recent meta-analysis with a median follow-up of 17 months has been performed (n=8595) but there was significant heterogeneity between the trials, highlighted in the discussion above, with differences in study population and treatments mentioned. There was no significant difference in the rate of

the composite outcome of cardiac death or myocardial infarction between the short (3-6 months) and prolonged (12-24 months DAPT groups (OR 1.11, 95% confidence interval 0.87 to 1.43, p=0.41). A landmark analysis performed at the time of discontinuation of DAPT demonstrated a non-significant higher rate of stent thrombosis in patients treated with a short course of DAPT (0.35% vs. 0.20%, p=0.22). The risk of major bleeding was higher with longer therapy (OR 1.97, 95% CI 2.97-28.62) (246).

More recent studies have looked at the implications of longer term DAPT, i.e. beyond the conventional 12 month period. Amongst these, the Dual AntiPlatelet Therapy (DAPT) study compared patients who had been successfully treated with 12 months of aspirin and a thienopyridine (either clopidogrel or prasugrel) to continue receiving the thienopyridine (n=5020) or placebo (n=4941) for another 18 months in addition to aspirin (247). Successful treatment was defined as freedom from all major adverse cardiovascular and cerebrovascular events (MACCE) or major bleeding events, repeat revascularisation and compliance with thienopyridine treatment. Enrolled patients had either stable (38 percent) or unstable disease. The rates for each of the co-primary end points of stent thrombosis and MACCE (a composite of death from any cause, MI, or stroke) were lower with continued thienopyridine therapy (0.4% vs. 1.4%; HR 0.29, 95% CI 0.17-0.48 and 4.3% vs. 5.9%; HR 0.71, 95% CI 0.59-0.85, respectively). The reduction in events with continued DAPT was mostly attributable to a lower rate of MI (2.1% vs. 4.1%; HR 0.47, p<0.001). With regards to the primary safety end point of moderate or severe bleeding applying the GUSTO criteria (248), this was increased with continued DAPT (2.5% vs. 1.6%, p = 0.001).

One of the headlines from the trial was that the rate of death from any cause was higher in the DAPT group (2.0% vs. 1.5%%; HR 1.36, 95% CI 1.00-1.85) which was due to an increase in non-cardiac deaths (1.0% vs. 0.5%, p=0.002). Another finding provided in the supplementary appendix of the trial was that there was an increased risk of MI during the three months following cessation of the thienopyridine therapy in both randomised groups.

The results of the DAPT study contrast with earlier smaller studies comparing DAPT beyond 12 months with aspirin alone. One study from South Korea combined the results of two trials, Correlation of Clopidogrel Therapy Discontinuation in Real-World Patients Treated with Drug-Eluting Stent Implantation and Late Coronary Arterial Thrombotic. Events (REAL-LATE) and Evaluation of the Long-Term Safety after Zotarolimus-Eluting Stent, Sirolimus-Eluting Stent, or Paclitaxel-Eluting Stent Implantation for Coronary Lesions - Late Coronary Arterial Thrombotic Events (ZEST-LATE). They had similar designs and due to slow recruitment, the data and safety committee agreed to merge the trials (249). Of 2701 patients recruited, the cumulative risk of the primary outcome (death or MI) at 2 years was 1.8% with dual antiplatelet therapy, as compared with 1.2% with aspirin monotherapy (HR, 1.65; 95% confidence interval [CI], 0.80 to 3.36; P=0.17). There was no significant difference in TIMI major bleeding (HR 2.96, 95% CI 0.31-28.6, p=0.35. In the Dual-antiplatelet treatment beyond 1 year after drug-eluting stent implantation (ARCTIC-Interruption) study, 1259 patients from multiple centres in France were randomly allocated to continued treatment with DAPT for 6-18 months or aspirin alone(250). Once again there was no significant difference in the primary endpoint of primary endpoint of death, MI, stent

thrombosis, stroke, or urgent revascularisation (4% for aspirin group vs. 4% for DAPT continuation group; HR 1·17,95% CI 0·68–2·03; p=0·58) after a median follow-up of 17 months. Major bleeding events occurred more often in the DAPT continuation group (seven [1%] patients) compared with the interruption group (one [<0·5%] patient; HR 0·15 [0·02–1·20]; p=0·073). A 2014 meta-analysis of these trials and four others (n = 12,536) found no difference in the rate of death (OR 1.18, 95% CI 0.61-2.29), but the risk of major bleeding was higher with longer therapy (OR 4.69, 95% CI 1.01-21.87) at a median follow-up of 17 months.

It is difficult to draw firm conclusions from these studies about the optimal duration of DAPT following DES implantation, particularly second generation DES. Although occurring at a lower frequency than with first generation DES, stent thrombosis remains a real concern. The trials discussed provide some reassurance concerning shorter courses of DAPT, but the larger DAPT trial suggests that there may be continuing cardiovascular benefits but achieved (as with most of these studies) at a higher risk of bleeding. The latest European revascularisation guidelines recommend DAPT for six months following elective DES implantation (251). Given these improvements, the focus on finding alternative strategies to DES has dissipated and research over the last few years has concentrated more on developing further improvements in DES platforms.

CHAPTER 8

Current and future directions

Although the scare around early and late stent thrombosis reinforced the need to examine other options to reduce the restenosis rates seen with stainless steel stents, the clinical research over the last 5-10 years, much of which is described in Section 7, led to developments in DES resulting in better and safer clinical results with DES. Given the fall in cost of DES, there are now fewer cases where there is a clinical impetus to use a bare metal stent. However, research to develop new technology to mitigate the pathogenic mechanisms behind the adverse events described continues. During the course of the SSTARS study, there have already been developments to try and build upon the success of second generation DES both in terms of reducing restenosis and improved safety. Broadly, these can be divided according to the components of a DES.

8.1 New polymer technology

The realisation that appropriate drug choice, along with optimised release kinetics were fundamental determinants affecting the long-term success of DES drove the development of the Resolute™ (Medtronic, Santa Rosa, California) -ZES (R-ZES), which has longer drug elution than the original Endeavor stent. Using the same cobalt chromium platform as E-ZES, R-ZES incorporated a new Biolinx polymer comprised of a hydrophobic C10 polymer to control drug release, a biocompatible and hydrophilic C19 polymer and polyvinyl pyrrolidone to allow an early burst of drug release. The polymer combinations also allowed delayed drug release, such that at least 85% of the zotarolimus was released within 60 days, with the remainder being released

within 180 days (252). E-ZES and R-ZES have not been directly compared but results from a study (n=139) that examined late lumen loss with single de novo coronary lesions suggested benefit from this polymer (253). At nine month follow-up, late loss was 0.22 +/- 0.27 mm with the R-ZES, which was lower than previously observed in E-ZES.

R-ZES has been compared to another durable biocompatible polymer stent, X-EES, in the TWENTE trial (254). This was a single bind (patient only), randomised non-inferiority trial involving 1391 patients. The primary composite endpoint of target vessel failure (cardiac death, target vessel related MI or clinically driven TVR) occurred in 8.2% for R-ZES and 8.1% for X-EES during 12 months follow up meeting the non inferiority margin (absolute risk difference of ≤4.48%). The definite-or-probable stent thrombosis rates were similar for R-ZES and X-EES (0.9% and 1.2%, respectively, p = 0.59).

8.2 New metal stent platforms

In the SSTARS study, the impact of cobalt chromium stents with regards to restenosis was investigated and no advantage was seen compared to stainless steel. However, there was no disadvantage and one of the advantages that this alloy offers in comparison to stainless steel was greater radial strength allowing production of thinner struts, which also has the potential to enhance trackability and deliverability. This premise has subsequently led to the development of platinum chromium alloy stents which have even greater radial strength. Platinum is also more dense than cobalt or stainless steel and therefore more radio-opaque. The Promus Element ™

(Boston Scientific, Natick, Massachusetts) used the same polymer eluting everolimus as X-EES with a platinum chromium platform. In the Prospective, Randomized, Multicenter Trial to Assess an Everolimus-Eluting Coronary Stent System [PROMUS Element] for the Treatment of up to Two De Novo Coronary Artery Lesions (PLATINUM) trial, the platinum chromium alloy was found to have similar efficacy and safety compared to its cobalt chromium counterpart (n=1530) (255). The 12-month rates of target lesion failure (a composite of target vessel-related cardiac death, target vessel-related myocardial infarction, or ischemia-driven target lesion revascularization) were 2.9 and 3.4 percent, respectively. By intention-to-treat, there were no significant differences between CoCr-EES and PtCr-EES in the 12-month rates of TLF (3.2% vs. 3.5%, p = 0.72), cardiac death or MI (2.5% vs. 2.0%, p = 0.56), TLR (1.9% vs. 1.9%, p = 0.96), or Academic Research Consortium definite or probable stent thrombosis (0.4% vs. 0.4%, p = 1.00).

8.3 Biodegradeable polymers

One of the proposed mechanisms for stent thrombosis in DES is chronic inflammation related to the polymer that houses the antiproliferative drug. Conventional DES have what is described as durable or permanent polymers and the impact of using more biocompatible durable polymers has already been highlighted (section 5.4). Another potential method to decrease the rate of very late stent thrombosis with DES is to remove the polymer altogether as a potential chronic inflammatory stimulus leaving the patient with the potential long term safety advantage of a BMS. This approach has been employed in a number of stents using different polymers and drugs.

Amongst these types of stents, one of the most widely used and tested is the BioMatrix® stent (Biosensors Inc., Newport Beach, CA, USA). This utilises a stainless steel platform, the sirolimus analogue biolimus, and a biodegradable poly-L-lactide (PLA) polymer that is applied only to the abluminal (outer) surface of the stent. The Limus Eluted From A Durable Versus ERodable Stent Coating (LEADERS) trial was a randomised non-inferiority trial of 1707 patients with both stable and unstable coronary artery disease. Patients were randomly assigned to either the Biomatrix biolimus eluting stent (BES) or to the first generation C-SES. At nine months, the Biomatrix BES was non-inferior to the C-SES for the primary composite end point of cardiac death, MI, or clinically indicated TVR (9.0% vs. 11.0% respectively; RR 0.88, 95% CI 0.64–1.19) (256). This was maintained at five years follow up (22.3% vs. 26.1%, respectively; RR 0.83, 95% CI 0.68-1.02) but, interestingly, a pre-specified secondary analysis of very late stent thrombosis at this juncture was in favour of the BES (0.7% vs. 2.5%; RR0.26, 95% CI 0.10-0.68) (257). This may reflect the late safety advantage of the biodegradeable polymer.

Another BES, the Nobori® stent (Terumo Corporation, Tokyo, Japan) also uses the same stainless steel platform and the abluminal PLA polymer as the Biomatrix stent above but differs in the delivery system, balloon and stent coating process. The fifth Scandinavian Organisation for Randomised Trials with clinical OUTcome (SORT OUT V) compared Nobori BES (n=1229) with C-SES (n=1239) with both stable and unstable coronary artery disease. Surprisingly, the BES was not non-inferior to C-SES at one year for the composite endpoint of cardiac death, MI and definite stent thrombosis (4.1% BES vs. 3.1% SES, p=0.06) (258). All of the components were numerically

higher with the Nobori BES but particularly so for definite stent thrombosis (9 0·7% vs. 0·2%,95% CI 0·0-1·1; p=0·034). In the Comparison of the Everolimus eluting with Biolimus A9 eluting stent (COMPARE II) eluting stent) study (n=2707), Nobori BES was found to be non-inferior to X-EES at 12 months for the composite endpoint of cardiac death, MI, and TVR (5.2% vs. 4.8% respectively; RR 1·07, 95% CI 0·75-1·52 ; p(non-inferiority)<0·0001) (259). The study designs and endpoints use in these BES studies were different and this makes direct comparisons difficult. Further studies and more long term safety data are needed before firm conclusions can be drawn.

Another stent with a biodegradable polymer that has been trialled is the Synergy™ stent (Boston Scientific) which utilizes a platinum chromium stent with an abluminal biodegradeable polymer (polylactic acid/polyglycolic acid) and elutes everolimus. The Evolution Everolimus-Eluting Monorail Coronary Stent System for the Treatment of a De Novo Atherosclerotic Lesion (EVOLVE) trial compared two dose formulations of the SYNERGY stent with the durable polymer platinum chromium EES (n=291). Patients were randomized 1:1:1 and at 30 days, there was a non-significant difference in the primary clinical endpoint of target lesion failure (death, target vessel MI, target lesion revascularization) which occurred in 0 percent, 1.1 percent, and 3.1 percent of patients in the durable polymer EES, SYNERGY, and SYNERGY half-dose groups, respectively. Angiographic follow up was also performed at six months and there was no difference between the three groups in the primary angiographic endpoint of in-stent late loss (0.15 ± 0.34 mm for durable polymer EES, 0.10 ± 0.25 mm for SYNERGY, and 0.13 ± 0.26 mm for SYNERGY half dose, p for noninferiority <0.001). No stent thromboses

occurred through six-month follow-up within this small group of patients (260). Similarly, the two year follow up results were comparable between the three groups, target lesion failure rates of 6.1% for the durable polymer EES, 5.5% for Synergy, and 5.2% for Synergy half dose (p=0.87) (261). At two years, target lesion failure (TLF) was 6.1% for PE vs. 5.5% for SYNERGY (p=0.87) and 5.2% for SYNERGY ½ dose (p=0.81). There were no significant differences between groups for cardiac death, repeat revascularisation, MI or stent thrombosis through two years.

8.4 Bioresorbable stents

Coronary stents were developed to reduce the risk of restenosis after balloon angioplasty. Their evolution through to the development of DES has been reviewed in chapter 1. They are essentially "scaffolds" and are required acutely to seal intimal tears and prevent recoil following arterial barotrauma. They subsequently prevent constrictive remodelling which occurs within 6 months of the procedure (262). An ideal situation would be one where a "scaffold" is only present during this period. This has led to the development of bioresorbable vascular stents. Amongst these, the Absorb bioresorbable vascular scaffold (Abbott Vascular) consists of a 150μm thick bioresorbable poly(l-lactide) scaffold (PLLA) with a 7μm thick bioresorbable poly(d,l-lactide) coating, which elutes everolimus (263). PLLA has other medical applications and has been used in absorbable sutures and orthopaedic plates and screws. In the coronary setting, it is absorbed after approximately two years (262). The main attraction of developing these stents is that the development of late adverse events after placement of permanent metallic stents can be avoided.

These include persistent inflammation, impaired vasomotion and neo-atherosclerosis.

The everolimus-eluting bioresorbable Absorb scaffold has been compared with an everolimus-eluting metallic counterpart in six randomized trials (264-269). Data from these trials including 2337 patients that were treated with everolimus-eluting bioresorbable non-metallic vascular scaffolds and 1401 with everolimus-eluting metallic stents have been included in a meta-analysis (270). AT 12 months, the risk of target lesion revascularization (primary efficacy outcome) was similar in the two groups (odds ratio [OR] 0.97, 95% CI 0.66-1.43) as was the risk of target lesion failure (OR 1.20, 95% CI 0.90-1.60), myocardial infarction (OR 1.36, 95% CI 0.98-1.89), and death (OR 0. 97, 95% CI 0.45-2.00). The risk of definite or probable stent thrombosis was higher in those treated with a bioresorbable vascular scaffold (OR 1.99, 95% CI 1.00-3.98).

The ABSORB III trial was the largest in the meta-analysis. It included 2008 patients with stable or unstable angina who were randomly assigned in a 2:1 ratio to receive an everolimus-eluting bioresorbable vascular scaffold or an everolimus-eluting cobalt chromium stent (267). Patients with acute myocardial infarction and specific complex lesions were excluded. There was no significant difference between the two groups in the rate of the primary outcome of target lesion failure (cardiac death, target vessel myocardial infarction, or ischaemia driven target lesion revascularization) at one year (7.8 versus 6.1 percent, respectively). Results for the individual components of the primary end point did not differ. Device thrombosis at one year occurred in 1.5 and 0.7 percent ($p = 0.13$ for superiority) of the two groups, respectively.

At present, the results of these studies suggest no advantage for efficacy with the emerging polymer, metal stent or bioresorbable stents compared with second generation DES. Bioresorbable stents had a higher rate of stent thrombosis at one year. These technologies have potential benefits but longer-term outcomes are needed. It is possible that an advantage will appear in due course.

Conclusion

As discussed, inflammation is a key process in restenosis and so systemic anti-inflammatory therapy is a potentially attractive approach of limiting this. Additionally, thinner stent struts have been associated with less restenosis and there has been a corresponding drive towards the production of thinner strut stents and the use of different alloys to facilitate this. There was a need for more randomised trial data in this area and this formed the basis for this study.

SSTARS showed that treating patients upstream with a moderately high dose of prednisolone to cover most of the period of inflammation associated with restenosis in BMS did not reduce the incidence of binary angiographic restenosis. In addition, there was no significant reduction in restenosis rates with stents composed of cobalt chromium alloy compared to stainless steel. There was also no relationship between higher levels of hs-CRP and restenosis. Whilst systemic therapy with Prednisolone did reduce hs-CRP levels, this was not associated with a reduction in restenosis.

The study adds important information in this subject area, albeit with a negative finding. The results help bring perspective to other trial results including meta-analyses which seemed to indicate a role for systemic anti-inflammatory therapy. The impact of stent alloy has not previously been investigated in this context and this is the largest study involving the use of systemic prednisolone to prevent restenosis. Drug-eluting stents now dominate the clinical landscape and this study supports the concept of local as opposed to systemic delivery of drugs to reduce restenosis and further

research should continue to focus on improvements in the stent platforms as well as drug delivery systems (see sections 8.1 - 8.4).

References

1. Gruntzig AR, Senning A, Siegenthaler WE. Nonoperative dilatation of coronary-artery stenosis: percutaneous transluminal coronary angioplasty. N Engl J Med. 1979 Jul 12;301(2):61-8.
2. Lincoff AM, Popma JJ, Ellis SG, Hacker JA, Topol EJ. Abrupt vessel closure complicating coronary angioplasty: clinical, angiographic and therapeutic profile. J Am Coll Cardiol. 1992 Apr;19(5):926-35.
3. Mabin TA, Holmes DR, Jr., Smith HC, Vlietstra RE, Bove AA, Reeder GS, et al. Intracoronary thrombus: role in coronary occlusion complicating percutaneous transluminal coronary angioplasty. J Am Coll Cardiol. 1985 Feb;5(2 Pt 1):198-202.
4. Cowley MJ, Dorros G, Kelsey SF, Van Raden M, Detre KM. Acute coronary events associated with percutaneous transluminal coronary angioplasty. Am J Cardiol. 1984 Jun 15;53(12):12C-6C.
5. Detre K, Holubkov R, Kelsey S, Cowley M, Kent K, Williams D, et al. Percutaneous transluminal coronary angioplasty in 1985-1986 and 1977-1981. The National Heart, Lung, and Blood Institute Registry. N Engl J Med. 1988 Feb 4;318(5):265-70.
6. Gruentzig AR, King SB, 3rd, Schlumpf M, Siegenthaler W. Long-term follow-up after percutaneous transluminal coronary angioplasty. The early Zurich experience. N Engl J Med. 1987 Apr 30;316(18):1127-32.
7. Leimgruber PP, Roubin GS, Hollman J, Cotsonis GA, Meier B, Douglas JS, et al. Restenosis after successful coronary angioplasty in patients with single-vessel disease. Circulation. 1986 Apr;73(4):710-7.
8. Haude M, Erbel R, Issa H, Meyer J. Quantitative analysis of elastic recoil after balloon angioplasty and after intracoronary implantation of balloon-expandable Palmaz-Schatz stents. J Am Coll Cardiol. 1993 Jan;21(1):26-34.
9. Lange RA, Willard JE, Hillis LD. Southwestern internal medicine conference: restenosis: the Achilles heel of coronary angioplasty. Am J Med Sci. 1993 Oct;306(4):265-75.

10. Libby P, Schwartz D, Brogi E, Tanaka H, Clinton SK. A cascade model for restenosis. A special case of atherosclerosis progression. Circulation. 1992 Dec;86(6 Suppl):III47-52.
11. Mintz GS, Popma JJ, Pichard AD, Kent KM, Satler LF, Wong C, et al. Arterial remodeling after coronary angioplasty: a serial intravascular ultrasound study. Circulation. 1996 Jul 1;94(1):35-43.
12. Tenaglia AN, Buller CE, Kisslo KB, Stack RS, Davidson CJ. Mechanisms of balloon angioplasty and directional coronary atherectomy as assessed by intracoronary ultrasound. J Am Coll Cardiol. 1992 Sep;20(3):685-91.
13. Safian RD, Gelbfish JS, Erny RE, Schnitt SJ, Schmidt DA, Baim DS. Coronary atherectomy. Clinical, angiographic, and histological findings and observations regarding potential mechanisms. Circulation. 1990 Jul;82(1):69-79.
14. Topol EJ, Leya F, Pinkerton CA, Whitlow PL, Hofling B, Simonton CA, et al. A comparison of directional atherectomy with coronary angioplasty in patients with coronary artery disease. The CAVEAT Study Group. N Engl J Med. 1993 Jul 22;329(4):221-7.
15. Adelman AG, Cohen EA, Kimball BP, Bonan R, Ricci DR, Webb JG, et al. A comparison of directional atherectomy with balloon angioplasty for lesions of the left anterior descending coronary artery. N Engl J Med. 1993 Jul 22;329(4):228-33.
16. Sigwart U, Puel J, Mirkovitch V, Joffre F, Kappenberger L. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. N Engl J Med. 1987 Mar 19;316(12):701-6.
17. Roubin GS, Cannon AD, Agrawal SK, Macander PJ, Dean LS, Baxley WA, et al. Intracoronary stenting for acute and threatened closure complicating percutaneous transluminal coronary angioplasty. Circulation. 1992 Mar;85(3):916-27.
18. Lincoff AM, Topol EJ, Chapekis AT, George BS, Candela RJ, Muller DW, et al. Intracoronary stenting compared with conventional therapy for abrupt vessel closure complicating coronary angioplasty: a matched case-control study. J Am Coll Cardiol. 1993 Mar 15;21(4):866-75.

19. Serruys PW, de Jaegere P, Kiemeneij F, Macaya C, Rutsch W, Heyndrickx G, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. N Engl J Med. 1994 Aug 25;331(8):489-95.
20. Fischman DL, Leon MB, Baim DS, Schatz RA, Savage MP, Penn I, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. N Engl J Med. 1994 Aug 25;331(8):496-501.
21. Cutlip DE, Chauhan MS, Baim DS, Ho KK, Popma JJ, Carrozza JP, et al. Clinical restenosis after coronary stenting: perspectives from multicenter clinical trials. J Am Coll Cardiol. 2002 Dec 18;40(12):2082-9.
22. Kuntz RE, Safian RD, Carrozza JP, Fishman RF, Mansour M, Baim DS. The importance of acute luminal diameter in determining restenosis after coronary atherectomy or stenting. Circulation. 1992 Dec;86(6):1827-35.
23. Sousa JE, Costa MA, Abizaid A, Abizaid AS, Feres F, Pinto IM, et al. Lack of neointimal proliferation after implantation of sirolimus-coated stents in human coronary arteries: a quantitative coronary angiography and three-dimensional intravascular ultrasound study. Circulation. 2001 Jan 16;103(2):192-5.
24. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med. 2002 Jun 6;346(23):1773-80.
25. Holmes DR, Jr., Leon MB, Moses JW, Popma JJ, Cutlip D, Fitzgerald PJ, et al. Analysis of 1-year clinical outcomes in the SIRIUS trial: a randomized trial of a sirolimus-eluting stent versus a standard stent in patients at high risk for coronary restenosis. Circulation. 2004 Feb 10;109(5):634-40.
26. McFadden EP, Stabile E, Regar E, Cheneau E, Ong AT, Kinnaird T, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. Lancet. 2004 Oct 23-29;364(9444):1519-21.
27. Mintz GS, Weissman NJ, Teirstein PS, Ellis SG, Waksman R, Russo RJ, et al. Effect of intracoronary gamma-radiation therapy on in-stent restenosis: An intravascular ultrasound analysis from the gamma-1 study. Circulation. 2000 Dec 12;102(24):2915-8.

28. Waksman R, White RL, Chan RC, Bass BG, Geirlach L, Mintz GS, et al. Intracoronary gamma-radiation therapy after angioplasty inhibits recurrence in patients with in-stent restenosis. Circulation. 2000 May 9;101(18):2165-71.
29. Waksman R, Rodriguez JC, Robinson KA, Cipolla GD, Crocker IR, Scott NA, et al. Effect of intravascular irradiation on cell proliferation, apoptosis, and vascular remodeling after balloon overstretch injury of porcine coronary arteries. Circulation. 1997 Sep 16;96(6):1944-52.
30. Stone GW, Ellis SG, O'Shaughnessy CD, Martin SL, Satler L, McGarry T, et al. Paclitaxel-eluting stents vs vascular brachytherapy for in-stent restenosis within bare-metal stents: the TAXUS V ISR randomized trial. JAMA. 2006 Mar 15;295(11):1253-63.
31. Holmes DR, Jr., Teirstein P, Satler L, Sketch M, O'Malley J, Popma JJ, et al. Sirolimus-eluting stents vs vascular brachytherapy for in-stent restenosis within bare-metal stents: the SISR randomized trial. JAMA. 2006 Mar 15;295(11):1264-73.
32. Roubin GS, King SB, 3rd, Douglas JS, Jr. Restenosis after percutaneous transluminal coronary angioplasty: the Emory University Hospital experience. Am J Cardiol. 1987 Jul 31;60(3):39B-43B.
33. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation. 2007 May 1;115(17):2344-51.
34. Gould KL LK, Hamilton GW. Physiologic basis for assessing critical coronary stenosis. Instantaneous flow response and regional distribution during coronary hyperemia as measures of coronary flow reserve. Am J Cardiol. 1974 1974;33:87-94.
35. Mehran R, Dangas G, Abizaid AS, Mintz GS, Lansky AJ, Satler LF, et al. Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. Circulation. 1999 Nov 2;100(18):1872-8.
36. Reiber JH, Kooijman CJ, Slager CJ, Gerbrands JJ, Schuurbiers JC, Den Boer A, et al. Coronary artery dimensions from cineangiograms methodology and validation of a computer-assisted analysis procedure. IEEE Trans Med Imaging. 1984;3(3):131-41.

37. Serruys PW, Reiber JH, Wijns W, van den Brand M, Kooijman CJ, ten Katen HJ, et al. Assessment of percutaneous transluminal coronary angioplasty by quantitative coronary angiography: diameter versus densitometric area measurements. Am J Cardiol. 1984 Sep 1;54(6):482-8.
38. Nallamothu BK, Spertus JA, Lansky AJ, Cohen DJ, Jones PG, Kureshi F, et al. Comparison of clinical interpretation with visual assessment and quantitative coronary angiography in patients undergoing percutaneous coronary intervention in contemporary practice: the Assessing Angiography (A2) project. Circulation. Apr 30;127(17):1793-800.
39. Goldberg RK, Kleiman NS, Minor ST, Abukhalil J, Raizner AE. Comparison of quantitative coronary angiography to visual estimates of lesion severity pre and post PTCA. Am Heart J. 1990 Jan;119(1):178-84.
40. Fleming RM, Kirkeeide RL, Smalling RW, Gould KL. Patterns in visual interpretation of coronary arteriograms as detected by quantitative coronary arteriography. J Am Coll Cardiol. 1991 Oct;18(4):945-51.
41. Peters RJ, Kok WE, Pasterkamp G, Von Birgelen C, Prins M, Serruys PW. Videodensitometric quantitative angiography after coronary balloon angioplasty, compared to edge-detection quantitative angiography and intracoronary ultrasound imaging. Eur Heart J. 2000 Apr;21(8):654-61.
42. Ross R, Glomset JA. The pathogenesis of atherosclerosis (first of two parts). N Engl J Med. 1976 Aug 12;295(7):369-77.
43. Libby P, Simon DI. Inflammation and thrombosis: the clot thickens. Circulation. 2001 Apr 3;103(13):1718-20.
44. Schwartz RS, Huber KC, Murphy JG, Edwards WD, Camrud AR, Vlietstra RE, et al. Restenosis and the proportional neointimal response to coronary artery injury: results in a porcine model. J Am Coll Cardiol. 1992 Feb;19(2):267-74.
45. Hoffmann R, Mintz GS, Dussaillant GR, Popma JJ, Pichard AD, Satler LF, et al. Patterns and mechanisms of in-stent restenosis. A serial intravascular ultrasound study. Circulation. 1996 Sep 15;94(6):1247-54.
46. Kearney M, Pieczek A, Haley L, Losordo DW, Andres V, Schainfeld R, et al. Histopathology of in-stent restenosis in patients with peripheral artery disease. Circulation. 1997 Apr 15;95(8):1998-2002.

47. Kornowski R, Hong MK, Tio FO, Bramwell O, Wu H, Leon MB. In-stent restenosis: contributions of inflammatory responses and arterial injury to neointimal hyperplasia. J Am Coll Cardiol. 1998 Jan;31(1):224-30.
48. Farb A, Sangiorgi G, Carter AJ, Walley VM, Edwards WD, Schwartz RS, et al. Pathology of acute and chronic coronary stenting in humans. Circulation. 1999 Jan 5-12;99(1):44-52.
49. Fuster V, Falk E, Fallon JT, Badimon L, Chesebro JH, Badimon JJ. The three processes leading to post PTCA restenosis: dependence on the lesion substrate. Thromb Haemost. 1995 Jul;74(1):552-9.
50. Owens GK, Kumar MS, Wamhoff BR. Molecular regulation of vascular smooth muscle cell differentiation in development and disease. Physiol Rev. 2004 Jul;84(3):767-801.
51. Stump MM, Jordan GL, Jr., Debakey ME, Halpert B. Endothelium Grown from Circulating Blood on Isolated Intravascular Dacron Hub. Am J Pathol. 1963 Sep;43:361-7.
52. Feigl W, Susani M, Ulrich W, Matejka M, Losert U, Sinzinger H. Organisation of experimental thrombosis by blood cells. Evidence of the transformation of mononuclear cells into myofibroblasts and endothelial cells. Virchows Arch A Pathol Anat Histopathol. 1985;406(2):133-48.
53. Campbell JH, Efendy JL, Campbell GR. Novel vascular graft grown within recipient's own peritoneal cavity. Circ Res. 1999 Dec 3-17;85(12):1173-8.
54. Han CI, Campbell GR, Campbell JH. Circulating bone marrow cells can contribute to neointimal formation. J Vasc Res. 2001 Mar-Apr;38(2):113-9.
55. Sata M, Saiura A, Kunisato A, Tojo A, Okada S, Tokuhisa T, et al. Hematopoietic stem cells differentiate into vascular cells that participate in the pathogenesis of atherosclerosis. Nat Med. 2002 Apr;8(4):403-9.
56. Sartore S, Chiavegato A, Faggin E, Franch R, Puato M, Ausoni S, et al. Contribution of adventitial fibroblasts to neointima formation and vascular remodeling: from innocent bystander to active participant. Circ Res. 2001 Dec 7;89(12):1111-21.
57. Dangas GD, Claessen BE, Caixeta A, Sanidas EA, Mintz GS, Mehran R. In-stent restenosis in the drug-eluting stent era. J Am Coll Cardiol. 2010 Nov 30;56(23):1897-907.

58. Abizaid A, Kornowski R, Mintz GS, Hong MK, Abizaid AS, Mehran R, et al. The influence of diabetes mellitus on acute and late clinical outcomes following coronary stent implantation. J Am Coll Cardiol. 1998 Sep;32(3):584-9.
59. Violaris AG, Melkert R, Serruys PW. Long-term luminal renarrowing after successful elective coronary angioplasty of total occlusions. A quantitative angiographic analysis. Circulation. 1995 Apr 15;91(8):2140-50.
60. Kastrati A, Schomig A, Elezi S, Schuhlen H, Dirschinger J, Hadamitzky M, et al. Predictive factors of restenosis after coronary stent placement. J Am Coll Cardiol. 1997 Nov 15;30(6):1428-36.
61. Kastrati A, Elezi S, Dirschinger J, Hadamitzky M, Neumann FJ, Schomig A. Influence of lesion length on restenosis after coronary stent placement. Am J Cardiol. 1999 Jun 15;83(12):1617-22.
62. Kastrati A, Schomig A, Elezi S, Dirschinger J, Mehilli J, Schuhlen H, et al. Prognostic value of the modified american college of Cardiology/American heart association stenosis morphology classification for long-term angiographic and clinical outcome after coronary stent placement. Circulation. 1999 Sep 21;100(12):1285-90.
63. Serruys PW, Kay IP, Disco C, Deshpande NV, de Feyter PJ. Periprocedural quantitative coronary angiography after Palmaz-Schatz stent implantation predicts the restenosis rate at six months: results of a meta-analysis of the BElgian NEtherlands Stent study (BENESTENT) I, BENESTENT II Pilot, BENESTENT II and MUSIC trials. Multicenter Ultrasound Stent In Coronaries. J Am Coll Cardiol. 1999 Oct;34(4):1067-74.
64. Pache J, Kastrati A, Mehilli J, Schuhlen H, Dotzer F, Hausleiter J, et al. Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STEREO-2) trial. J Am Coll Cardiol. 2003 Apr 16;41(8):1283-8.
65. Kobayashi Y, De Gregorio J, Kobayashi N, Akiyama T, Reimers B, Finci L, et al. Stented segment length as an independent predictor of restenosis. J Am Coll Cardiol. 1999 Sep;34(3):651-9.
66. Kastrati A, Schomig A, Elezi S, Schuhlen H, Wilhelm M, Dirschinger J. Interlesion dependence of the risk for restenosis in patients with coronary

stent placement in in multiple lesions. Circulation. 1998 Jun 23;97(24):2396-401.
67. Singh M, Gersh BJ, McClelland RL, Ho KK, Willerson JT, Penny WF, et al. Clinical and angiographic predictors of restenosis after percutaneous coronary intervention: insights from the Prevention of Restenosis With Tranilast and Its Outcomes (PRESTO) trial. Circulation. 2004 Jun 8;109(22):2727-31.
68. Castagna MT, Mintz GS, Leiboff BO, Ahmed JM, Mehran R, Satler LF, et al. The contribution of "mechanical" problems to in-stent restenosis: An intravascular ultrasonographic analysis of 1090 consecutive in-stent restenosis lesions. Am Heart J. 2001 Dec;142(6):970-4.
69. Lemos PA, Hoye A, Goedhart D, Arampatzis CA, Saia F, van der Giessen WJ, et al. Clinical, angiographic, and procedural predictors of angiographic restenosis after sirolimus-eluting stent implantation in complex patients: an evaluation from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) study. Circulation. 2004 Mar 23;109(11):1366-70.
70. Costa MA, Simon DI. Molecular basis of restenosis and drug-eluting stents. Circulation. 2005 May 3;111(17):2257-73.
71. Stettler C, Wandel S, Allemann S, Kastrati A, Morice MC, Schomig A, et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. Lancet. 2007 Sep 15;370(9591):937-48.
72. Nordmann AJ, Briel M, Bucher HC. Mortality in randomized controlled trials comparing drug-eluting vs. bare metal stents in coronary artery disease: a meta-analysis. Eur Heart J. 2006 Dec;27(23):2784-814.
73. Camenzind E, Steg PG, Wijns W. Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern. Circulation. 2007 Mar 20;115(11):1440-55; discussion 55.
74. Serruys PW, Daemen J. Are drug-eluting stents associated with a higher rate of late thrombosis than bare metal stents? Late stent thrombosis: a nuisance in both bare metal and drug-eluting stents. Circulation. 2007 Mar 20;115(11):1433-9; discussion 9.
75. Pfisterer M, Brunner-La Rocca HP, Buser PT, Rickenbacher P, Hunziker P, Mueller C, et al. Late clinical events after clopidogrel

discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. J Am Coll Cardiol. 2006 Dec 19;48(12):2584-91.
76. Finn AV, Joner M, Nakazawa G, Kolodgie F, Newell J, John MC, et al. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. Circulation. 2007 May 8;115(18):2435-41.
77. Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol. 2006 Jul 4;48(1):193-202.
78. Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, et al. Guidelines on myocardial revascularization. Eur Heart J. Oct;31(20):2501-55.
79. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation. Dec 6;124(23):e574-651.
80. Aoki J, Colombo A, Dudek D, Banning AP, Drzewiecki J, Zmudka K, et al. Peristent remodeling and neointimal suppression 2 years after polymer-based, paclitaxel-eluting stent implantation: insights from serial intravascular ultrasound analysis in the TAXUS II study. Circulation. 2005 Dec 20;112(25):3876-83.
81. Aoki J, Abizaid AC, Serruys PW, Ong AT, Boersma E, Sousa JE, et al. Evaluation of four-year coronary artery response after sirolimus-eluting stent implantation using serial quantitative intravascular ultrasound and computer-assisted grayscale value analysis for plaque composition in event-free patients. J Am Coll Cardiol. 2005 Nov 1;46(9):1670-6.
82. Cutlip DE, Chhabra AG, Baim DS, Chauhan MS, Marulkar S, Massaro J, et al. Beyond restenosis: five-year clinical outcomes from second-generation coronary stent trials. Circulation. 2004 Sep 7;110(10):1226-30.
83. Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med. 2004 Jan 15;350(3):221-31.

84. Mauri L, Orav EJ, O'Malley AJ, Moses JW, Leon MB, Holmes DR, Jr., et al. Relationship of late loss in lumen diameter to coronary restenosis in sirolimus-eluting stents. Circulation. 2005 Jan 25;111(3):321-7.
85. Inoue K, Abe K, Ando K, Shirai S, Nishiyama K, Nakanishi M, et al. Pathological analyses of long-term intracoronary Palmaz-Schatz stenting; Is its efficacy permanent? Cardiovasc Pathol. 2004 Mar-Apr;13(2):109-15.
86. Hasegawa K, Tamai H, Kyo E, Kosuga K, Ikeguchi S, Hata T, et al. Histopathological findings of new in-stent lesions developed beyond five years. Catheter Cardiovasc Interv. 2006 Oct;68(4):554-8.
87. Nakazawa G, Vorpahl M, Finn AV, Narula J, Virmani R. One step forward and two steps back with drug-eluting-stents: from preventing restenosis to causing late thrombosis and nouveau atherosclerosis. JACC Cardiovasc Imaging. 2009 May;2(5):625-8.
88. Chen MS, John JM, Chew DP, Lee DS, Ellis SG, Bhatt DL. Bare metal stent restenosis is not a benign clinical entity. Am Heart J. 2006 Jun;151(6):1260-4.
89. Rathore S, Kinoshita Y, Terashima M, Katoh O, Matsuo H, Tanaka N, et al. A comparison of clinical presentations, angiographic patterns and outcomes of in-stent restenosis between bare metal stents and drug eluting stents. EuroIntervention. Feb;5(7):841-6.
90. Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet. 2008 Aug 9;372(9637):449-56.
91. Garcia-Touchard A, Burke SE, Toner JL, Cromack K, Schwartz RS. Zotarolimus-eluting stents reduce experimental coronary artery neointimal hyperplasia after 4 weeks. Eur Heart J. 2006 Apr;27(8):988-93.
92. Grube E, Buellesfeld L. BioMatrix Biolimus A9-eluting coronary stent: a next-generation drug-eluting stent for coronary artery disease. Expert Rev Med Devices. 2006 Nov;3(6):731-41.
93. Garg S, Serruys PW. Coronary Stents: Looking Forward. Journal of the American College of Cardiology.56(10, Supplement):S43-S78.
94. Walker BR. Glucocorticoids and cardiovascular disease. Eur J Endocrinol. 2007 Nov;157(5):545-59.

95. Sapolsky RM, Romero LM, Munck AU. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocr Rev. 2000 Feb;21(1):55-89.
96. Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids--new mechanisms for old drugs. N Engl J Med. 2005 Oct 20;353(16):1711-23.
97. Stewart PM, Krozowski ZS. 11 beta-Hydroxysteroid dehydrogenase. Vitam Horm. 1999;57:249-324.
98. Seckl JR, Walker BR. Minireview: 11beta-hydroxysteroid dehydrogenase type 1- a tissue-specific amplifier of glucocorticoid action. Endocrinology. 2001 Apr;142(4):1371-6.
99. Whitworth JA, Mangos GJ, Kelly JJ. Cushing, cortisol, and cardiovascular disease. Hypertension. 2000 Nov;36(5):912-6.
100. Longenecker JP, Kilty LA, Johnson LK. Glucocorticoid inhibition of vascular smooth muscle cell proliferation: influence of homologous extracellular matrix and serum mitogens. J Cell Biol. 1984 Feb;98(2):534-40.
101. Voisard R, Seitzer U, Baur R, Dartsch PC, Osterhues H, Hoher M, et al. Corticosteroid agents inhibit proliferation of smooth muscle cells from human atherosclerotic arteries in vitro. Int J Cardiol. 1994 Mar 1;43(3):257-67.
102. Radke PW, Weber C, Kaiser A, Schober A, Hoffmann R. Dexamethasone and restenosis after coronary stent implantation: new indication for an old drug? Curr Pharm Des. 2004;10(4):349-55.
103. Idriss HT, Naismith JH. TNF alpha and the TNF receptor superfamily: structure-function relationship(s). Microsc Res Tech. 2000 Aug 1;50(3):184-95.
104. Beutler B, Krochin N, Milsark IW, Luedke C, Cerami A. Control of cachectin (tumor necrosis factor) synthesis: mechanisms of endotoxin resistance. Science. 1986 May 23;232(4753):977-80.
105. Monaco C, Paleolog E. Nuclear factor kappaB: a potential therapeutic target in atherosclerosis and thrombosis. Cardiovasc Res. 2004 Mar 1;61(4):671-82.
106. De Bosscher K, Schmitz ML, Vanden Berghe W, Plaisance S, Fiers W, Haegeman G. Glucocorticoid-mediated repression of nuclear factor-kappaB-dependent transcription involves direct interference with transactivation. Proc Natl Acad Sci U S A. 1997 Dec 9;94(25):13504-9.

107. Mukaida N, Zachariae CC, Gusella GL, Matsushima K. Dexamethasone inhibits the induction of monocyte chemotactic-activating factor production by IL-1 or tumor necrosis factor. J Immunol. 1991 Feb 15;146(4):1212-5.
108. Standiford TJ, Kunkel SL, Rolfe MW, Evanoff HL, Allen RM, Strieter RM. Regulation of human alveolar macrophage- and blood monocyte-derived interleukin-8 by prostaglandin E2 and dexamethasone. Am J Respir Cell Mol Biol. 1992 Jan;6(1):75-81.
109. Cronstein BN, Kimmel SC, Levin RI, Martiniuk F, Weissmann G. A mechanism for the antiinflammatory effects of corticosteroids: the glucocorticoid receptor regulates leukocyte adhesion to endothelial cells and expression of endothelial-leukocyte adhesion molecule 1 and intercellular adhesion molecule 1. Proc Natl Acad Sci U S A. 1992 Nov 1;89(21):9991-5.
110. Aziz KE, Wakefield D. Modulation of endothelial cell expression of ICAM-1, E-selectin, and VCAM-1 by beta-estradiol, progesterone, and dexamethasone. Cell Immunol. 1996 Jan 10;167(1):79-85.
111. Simoncini T, Maffei S, Basta G, Barsacchi G, Genazzani AR, Liao JK, et al. Estrogens and glucocorticoids inhibit endothelial vascular cell adhesion molecule-1 expression by different transcriptional mechanisms. Circ Res. 2000 Jul 7;87(1):19-25.
112. Wingett D, Forcier K, Nielson CP. Glucocorticoid-mediated inhibition of RANTES expression in human T lymphocytes. FEBS Lett. 1996 Dec 2;398(2-3):308-11.
113. Kwon OJ, Jose PJ, Robbins RA, Schall TJ, Williams TJ, Barnes PJ. Glucocorticoid inhibition of RANTES expression in human lung epithelial cells. Am J Respir Cell Mol Biol. 1995 May;12(5):488-96.
114. Schober A, Manka D, von Hundelshausen P, Huo Y, Hanrath P, Sarembock IJ, et al. Deposition of platelet RANTES triggering monocyte recruitment requires P-selectin and is involved in neointima formation after arterial injury. Circulation. 2002 Sep 17;106(12):1523-9.
115. Heyderman RS, Klein NJ, Daramola OA, Levin M. Modulation of the endothelial procoagulant response to lipopolysaccharide and tumour necrosis factor-alpha in-vitro: the effects of dexamethasone, pentoxifylline, iloprost and

a polyclonal anti-human IL-1 alpha antibody. Inflamm Res. 1995 Jul;44(7):275-80.
116. Gray E, Thomas S, Mistry Y, Poole S. Inhibition of tissue factor and cytokine release. Haemostasis. 1996;26 Suppl 1:92-5.
117. Perlman H, Maillard L, Krasinski K, Walsh K. Evidence for the rapid onset of apoptosis in medial smooth muscle cells after balloon injury. Circulation. 1997 Feb 18;95(4):981-7.
118. Hanke H, Strohschneider T, Oberhoff M, Betz E, Karsch KR. Time course of smooth muscle cell proliferation in the intima and media of arteries following experimental angioplasty. Circ Res. 1990 Sep;67(3):651-9.
119. Erl W, Hansson GK, de Martin R, Draude G, Weber KS, Weber C. Nuclear factor-kappa B regulates induction of apoptosis and inhibitor of apoptosis protein-1 expression in vascular smooth muscle cells. Circ Res. 1999 Apr 2;84(6):668-77.
120. Thompson EB. Apoptosis and steroid hormones. Mol Endocrinol. 1994 Jun;8(6):665-73.
121. Hadoke PW, Iqbal J, Walker BR. Therapeutic manipulation of glucocorticoid metabolism in cardiovascular disease. Br J Pharmacol. 2009 Mar;156(5):689-712.
122. Stone GW, Rutherford BD, McConahay DR, Johnson WL, Giorgi LV, Ligon RW, et al. A randomized trial of corticosteroids for the prevention of restenosis in 102 patients undergoing repeat coronary angioplasty. Cathet Cardiovasc Diagn. 1989 Dec;18(4):227-31.
123. Pepine CJ, Hirshfeld JW, Macdonald RG, Henderson MA, Bass TA, Goldberg S, et al. A controlled trial of corticosteroids to prevent restenosis after coronary angioplasty. M-HEART Group. Circulation. 1990 Jun;81(6):1753-61.
124. Lee CW, Chae JK, Lim HY, Hong MK, Kim JJ, Park SW, et al. Prospective randomized trial of corticosteroids for the prevention of restenosis after intracoronary stent implantation. Am Heart J. 1999 Jul;138(1 Pt 1):60-3.
125. Versaci F, Gaspardone A, Tomai F, Ribichini F, Russo P, Proietti I, et al. Immunosuppressive Therapy for the Prevention of Restenosis after Coronary Artery Stent Implantation (IMPRESS Study). J Am Coll Cardiol. 2002 Dec 4;40(11):1935-42.

126. Reimers B, Moussa II, Akiyama T, Kobayashi Y, Albiero R, Di Francesco L, et al. Persistent High Restenosis After Local Intrawall Delivery of Long-Acting Steroids Before Coronary Stent Implantation. J Invasive Cardiol. 1998 Jul;10(6):323-31.
127. Liu X, Huang Y, Hanet C, Vandormael M, Legrand V, Dens J, et al. Study of antirestenosis with the BiodivYsio dexamethasone-eluting stent (STRIDE): a first-in-human multicenter pilot trial. Catheter Cardiovasc Interv. 2003 Oct;60(2):172-8; discussion 9.
128. Hoffmann R, Langenberg R, Radke P, Franke A, Blindt R, Ortlepp J, et al. Evaluation of a high-dose dexamethasone-eluting stent. Am J Cardiol. 2004 Jul 15;94(2):193-5.
129. Fishel RS, Eisenberg S, Shai SY, Redden RA, Bernstein KE, Berk BC. Glucocorticoids induce angiotensin-converting enzyme expression in vascular smooth muscle. Hypertension. 1995 Mar;25(3):343-9.
130. Kato H, Hayashi T, Koshino Y, Oida K, Kutsumi Y, Nakai T, et al. Autocrine production of endothelin-1 participates in the glucocorticoid-induced Ca2+ influx into vascular smooth muscle cells. Biochem Biophys Res Commun. 1995 Mar 8;208(1):82-8.
131. Iuchi T, Akaike M, Mitsui T, Ohshima Y, Shintani Y, Azuma H, et al. Glucocorticoid excess induces superoxide production in vascular endothelial cells and elicits vascular endothelial dysfunction. Circ Res. 2003 Jan 10;92(1):81-7.
132. Grossman A, Johannsson G, Quinkler M, Zelissen P. Therapy of endocrine disease: Perspectives on the management of adrenal insufficiency: clinical insights from across Europe. Eur J Endocrinol. Dec;169(6):R165-75.
133. Libby P, Warner SJ, Friedman GB. Interleukin 1: a mitogen for human vascular smooth muscle cells that induces the release of growth-inhibitory prostanoids. J Clin Invest. 1988 Feb;81(2):487-98.
134. Gauldie J, Richards C, Harnish D, Lansdorp P, Baumann H. Interferon beta 2/B-cell stimulatory factor type 2 shares identity with monocyte-derived hepatocyte-stimulating factor and regulates the major acute phase protein response in liver cells. Proc Natl Acad Sci U S A. 1987 Oct;84(20):7251-5.
135. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. J Clin Invest. 2003 Jun;111(12):1805-12.

136. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO, 3rd, Criqui M, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation. 2003 Jan 28;107(3):499-511.
137. Gaspardone A, Crea F, Versaci F, Tomai F, Pellegrino A, Chiariello L, et al. Predictive value of C-reactive protein after successful coronary-artery stenting in patients with stable angina. Am J Cardiol. 1998 Aug 15;82(4):515-8.
138. Buffon A, Liuzzo G, Biasucci LM, Pasqualetti P, Ramazzotti V, Rebuzzi AG, et al. Preprocedural serum levels of C-reactive protein predict early complications and late restenosis after coronary angioplasty. J Am Coll Cardiol. 1999 Nov 1;34(5):1512-21.
139. Walter DH, Fichtlscherer S, Sellwig M, Auch-Schwelk W, Schachinger V, Zeiher AM. Preprocedural C-reactive protein levels and cardiovascular events after coronary stent implantation. J Am Coll Cardiol. 2001 Mar 1;37(3):839-46.
140. Kawamoto R, Hatakeyama K, Imamura T, Ishikawa T, Date H, Shibata Y, et al. Relation of C-reactive protein to restenosis after coronary stent implantation and to restenosis after coronary atherectomy. The American Journal of Cardiology. 2004;94(1):104-7.
141. Zhou YF, Csako G, Grayston JT, Wang SP, Yu ZX, Shou M, et al. Lack of association of restenosis following coronary angioplasty with elevated C-reactive protein levels or seropositivity to Chlamydia pneumoniae. Am J Cardiol. 1999 Sep 1;84(5):595-8, A8.
142. Horne BD, Muhlestein JB, Strobel GG, Carlquist JF, Bair TL, Anderson JL. Greater pathogen burden but not elevated C-reactive protein increases the risk of clinical restenosis after percutaneous coronary intervention. Am Heart J. 2002 Sep;144(3):491-500.
143. Ballou SP, Lozanski G. Induction of inflammatory cytokine release from cultured human monocytes by C-reactive protein. Cytokine. 1992 Sep;4(5):361-8.

144. Xie L, Chang L, Guan Y, Wang X. C-reactive protein augments interleukin-8 secretion in human peripheral blood monocytes. J Cardiovasc Pharmacol. 2005 Nov;46(5):690-6.
145. Verma S, Li SH, Badiwala MV, Weisel RD, Fedak PW, Li RK, et al. Endothelin antagonism and interleukin-6 inhibition attenuate the proatherogenic effects of C-reactive protein. Circulation. 2002 Apr 23;105(16):1890-6.
146. Liang YJ, Shyu KG, Wang BW, Lai LP. C-reactive protein activates the nuclear factor-kappaB pathway and induces vascular cell adhesion molecule-1 expression through CD32 in human umbilical vein endothelial cells and aortic endothelial cells. J Mol Cell Cardiol. 2006 Mar;40(3):412-20.
147. Liu C, Wang S, Deb A, Nath KA, Katusic ZS, McConnell JP, et al. Proapoptotic, antimigratory, antiproliferative, and antiangiogenic effects of commercial C-reactive protein on various human endothelial cell types in vitro: implications of contaminating presence of sodium azide in commercial preparation. Circ Res. 2005 Jul 22;97(2):135-43.
148. Dernellis J, Panaretou M. Relationship between C-reactive protein concentrations during glucocorticoid therapy and recurrent atrial fibrillation. Eur Heart J. 2004 Jul;25(13):1100-7.
149. Liakopoulos OJ, Schmitto JD, Kazmaier S, BrÃ¤uer A, Quintel M, Schoendube FA, et al. Cardiopulmonary and systemic effects of methylprednisolone in patients undergoing cardiac surgery. The Annals of thoracic surgery. 2007;84(1):110-9.
150. Brotman DJ, Girod JP, Garcia MJ, Patel JV, Gupta M, Posch A, et al. Effects of short-term glucocorticoids on cardiovascular biomarkers. J Clin Endocrinol Metab. 2005 Jun;90(6):3202-8.
151. Rogers C, Edelman ER. Endovascular stent design dictates experimental restenosis and thrombosis. Circulation. 1995 Jun 15;91(12):2995-3001.
152. Colombo A, Stankovic G, Moses JW. Selection of coronary stents. J Am Coll Cardiol. 2002 Sep 18;40(6):1021-33.
153. Morton AC, Crossman D, Gunn J. The influence of physical stent parameters upon restenosis. Pathol Biol (Paris). 2004 May;52(4):196-205.

154. Butany J, Carmichael K, Leong SW, Collins MJ. Coronary artery stents: identification and evaluation. J Clin Pathol. 2005 Aug;58(8):795-804.
155. Balcon R, Beyar R, Chierchia S, De Scheerder I, Hugenholtz PG, Kiemeneij F, et al. Recommendations on stent manufacture, implantation and utilization. Study Group of the Working Group on Coronary Circulation. Eur Heart J. 1997 Oct;18(10):1536-47.
156. Mani G, Feldman MD, Patel D, Agrawal CM. Coronary stents: A materials perspective. Biomaterials. 2007;28(9):1689-710.
157. Hara H, Nakamura M, Palmaz JC, Schwartz RS. Role of stent design and coatings on restenosis and thrombosis. Advanced Drug Delivery Reviews. 2006;58(3):377-86.
158. Barragan P, Rieu R, Garitey V, Roquebert PO, Sainsous J, Silvestri M, et al. Elastic recoil of coronary stents: a comparative analysis. Catheter Cardiovasc Interv. 2000 May;50(1):112-9.
159. Ormiston JA, Dixon SR, Webster MW, Ruygrok PN, Stewart JT, Minchington I, et al. Stent longitudinal flexibility: a comparison of 13 stent designs before and after balloon expansion. Catheter Cardiovasc Interv. 2000 May;50(1):120-4.
160. Serruys PW, Rensing B. Handbook of coronary stents. Third ed. London: Dunitz; 1998.
161. Konig A, Schiele TM, Rieber J, Theisen K, Mudra H, Klauss V. Stent design-related coronary artery remodeling and patterns of neointima formation following self-expanding and balloon-expandable stent implantation. Catheter Cardiovasc Interv. 2002 Aug;56(4):478-86.
162. Hong MK, Beyar R, Kornowski R, Tio FO, Bramwell O, Leon MB. Acute and chronic effects of self-expanding nitinol stents in porcine coronary arteries. Coron Artery Dis. 1997 Jan;8(1):45-8.
163. Serruys PW, Strauss BH, Beatt KJ, Bertrand ME, Puel J, Rickards AF, et al. Angiographic follow-up after placement of a self-expanding coronary-artery stent. N Engl J Med. 1991 Jan 3;324(1):13-7.
164. Schatz RA, Palmaz JC, Tio FO, Garcia F, Garcia O, Reuter SR. Balloon-expandable intracoronary stents in the adult dog. Circulation. 1987 Aug;76(2):450-7.

165. Serruys PW, Kutryk MJ, Ong AT. Coronary-artery stents. N Engl J Med. 2006 Feb 2;354(5):483-95.
166. White CJ. Stent recoil: comparison of the Wiktor-GX coil and the Palmaz-Schatz tubular coronary stent. Cathet Cardiovasc Diagn. 1997 May;41(1):1-3; discussion 4.
167. Lansky AJ, Roubin GS, Oâ€™Shaughnessy CD, Moore PB, Dean LS, Raizner AE, et al. Randomized comparison of GR-II stent and Palmaz-Schatz stent for elective treatment of coronary stenoses. Circulation. 2000;102(12):1364-8.
168. Thuesen L, Andersen HR, Krusell LR, Botker HE, Jorgensen E, Kelbaek H, et al. Randomized comparison of the coil-design Crossflex and the tubular NIR stent. Catheter Cardiovasc Interv. 2003 May;59(1):8-12.
169. Carrozza Jr JP, Hermiller Jr JB, Linnemeier TJ, Popma JJ, Yock PG, Roubin GS, et al. Quantitative Coronary Angiographic and Intravascular Ultrasound Assessment of a New Nonarticulated Stent: Report From the Advanced Cardiovascular Systems MultiLink Stent Pilot Study. Journal of the American College of Cardiology. 1998;31(1):50-6.
170. Baim DS, Cutlip DE, Midei M, Linnemeier TJ, Schreiber T, Cox D, et al. Final results of a randomized trial comparing the MULTI-LINK stent with the Palmaz-Schatz stent for narrowings in native coronary arteries. Am J Cardiol. 2001 Jan 15;87(2):157-62.
171. Kastrati A, Dirschinger J, Boekstegers P, Elezi S, Schuhlen H, Pache J, et al. Influence of stent design on 1-year outcome after coronary stent placement: a randomized comparison of five stent types in 1,147 unselected patients. Catheter Cardiovasc Interv. 2000 Jul;50(3):290-7.
172. Hoffmann R, Jansen C, Konig A, Haager PK, Kerckhoff G, vom Dahl J, et al. Stent design related neointimal tissue proliferation in human coronary arteries; an intravascular ultrasound study. Eur Heart J. 2001 Nov;22(21):2007-14.
173. Kastrati A, Mehilli J, Dirschinger J, Dotzer F, Schuhlen H, Neumann FJ, et al. Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STEREO) trial. Circulation. 2001 Jun 12;103(23):2816-21.

174. Hausleiter J, Kastrati A, Mehilli J, Schuhlen H, Pache J, Dotzer F, et al. Impact of lesion complexity on the capacity of a trial to detect differences in stent performance: results from the ISAR-STEREO trial. Am Heart J. 2003 Nov;146(5):882-6.
175. Rittersma SZ, de Winter RJ, Koch KT, Bax M, Schotborgh CE, Mulder KJ, et al. Impact of strut thickness on late luminal loss after coronary artery stent placement. Am J Cardiol. 2004 Feb 15;93(4):477-80.
176. Kereiakes DJ, Cox DA, Hermiller JB, Midei MG, Bachinsky WB, Nukta ED, et al. Usefulness of a cobalt chromium coronary stent alloy. Am J Cardiol. 2003 Aug 15;92(4):463-6.
177. Koster R, Vieluf D, Kiehn M, Sommerauer M, Kahler J, Baldus S, et al. Nickel and molybdenum contact allergies in patients with coronary in-stent restenosis. Lancet. 2000 Dec 2;356(9245):1895-7.
178. Hanawa T. Metal ion release from metal implants. Materials Science and Engineering: C. 2004;24(6â€“8):745-52.
179. Kastrati A, Schomig A, Dirschinger J, Mehilli J, von Welser N, Pache J, et al. Increased risk of restenosis after placement of gold-coated stents: results of a randomized trial comparing gold-coated with uncoated steel stents in patients with coronary artery disease. Circulation. 2000 May 30;101(21):2478-83.
180. Reifart N, Morice MC, Silber S, Benit E, Hauptmann KE, de Sousa E, et al. The NUGGET study: NIR ultra gold-gilded equivalency trial. Catheter Cardiovasc Interv. 2004 May;62(1):18-25.
181. Airoldi F, Colombo A, Tavano D, Stankovic G, Klugmann S, Paolillo V, et al. Comparison of diamond-like carbon-coated stents versus uncoated stainless steel stents in coronary artery disease. Am J Cardiol. 2004 Feb 15;93(4):474-7.
182. Unverdorben M, Sattler K, Degenhardt R, Fries R, Abt B, Wagner E, et al. Comparison of a silicon carbide coated stent versus a noncoated stent in humans: the Tenax- versus Nir-Stent Study (TENISS). J Interv Cardiol. 2003 Aug;16(4):325-33.
183. Di Mario C, Grube E, Nisanci Y, Reifart N, Colombo A, Rodermann J, et al. MOONLIGHT: a controlled registry of an iridium oxide-coated stent with angiographic follow-up. Int J Cardiol. 2004 Jun;95(2-3):329-31.

184. Windecker S, Simon R, Lins M, Klauss V, Eberli FR, Roffi M, et al. Randomized comparison of a titanium-nitride-oxide-coated stent with a stainless steel stent for coronary revascularization: the TiNOX trial. Circulation. 2005 May 24;111(20):2617-22.
185. Wohrle J, Al-Khayer E, Grotzinger U, Schindler C, Kochs M, Hombach V, et al. Comparison of the heparin coated vs the uncoated Jostent--no influence on restenosis or clinical outcome. Eur Heart J. 2001 Oct;22(19):1808-16.
186. Haude M, Konorza TF, Kalnins U, Erglis A, Saunamaki K, Glogar HD, et al. Heparin-coated stent placement for the treatment of stenoses in small coronary arteries of symptomatic patients. Circulation. 2003 Mar 11;107(9):1265-70.
187. Moses JW, Buller CE, Nukta ED. The first clinical trial comparing a coated versus a noncoated coronary stent: the Biocompatibles BiodivYsio stent in randomized control trial (DISTINCT). Circulation. 2000;101 (Suppl II):664.
188. Garg S, Serruys PW. Coronary Stents: Looking Forward. Journal of the American College of Cardiology. 2010;56(10, Supplement):S43-S78.
189. Medical Devices at the US Food and Drug Administration website. MULTI-LINK VISION™ RX & OTW Coronary Stent System - P020047. FDA website; 2003 [updated 2003; cited]; Available from: http://www.fda.gov/medicaldevices/productsandmedicalprocedures/deviceapprovalsandclearances/recently-approveddevices/ucm082409.htm.
190. MULTI-LINK ZETA® Coronary Stent Systems Information for Prescribers Abbot Vascular; 2008 [updated 2008; cited 23/05/2014]; Available from: http://www.abbottvascular.com/static/cms_workspace/pdf/ifu/coronary_intervention/MULTI-LINK_ZETA_Coronary_Stent_System.pdf.
191. Kereiakes D, Linnemeier TJ, Baim DS, Kuntz R, O'Shaughnessy C, Hermiller J, et al. Usefulness of stent length in predicting in-stent restenosis (the MULTI-LINK stent trials). Am J Cardiol. 2000 Aug 1;86(3):336-41.
192. Voratas K, Bruce WS. Binomial random variate generation. Commun ACM. 1988;31(2):216-22.

193. Sketch MH, Jr., Ball M, Rutherford B, Popma JJ, Russell C, Kereiakes DJ. Evaluation of the Medtronic (Driver) cobalt-chromium alloy coronary stent system. Am J Cardiol. 2005 Jan 1;95(1):8-12.
194. Hsieh FY, Lavori PW, Cohen HJ, Feussner JR. An overview of variance inflation factors for sample-size calculation. Eval Health Prof. 2003 Sep;26(3):239-57.
195. Fisher LD, Dixon DO, Herson J, Frankowski RK, Hearron MS, Peace KE. Intention to treat in clinical trials. Peace KE, editor. New York: Marcel Dekker; 1990.
196. Hennekens CH BJ, Mayrent SL. Epidemiology in Medicine. Boston: Little, Brown; 1987.
197. Fleiss JL. Statistical methods for rates and proportions. Second ed. Fleiss JL, editor. New York: John Wiley and Sons; 1981.
198. Molenberghs G, Verbeke G. Linear mixed models for longitudinal data. Molenberghs G, Verbeke G, editors. New York: Springer-Verlaf; 2000.
199. Graybill FA. An Introduction to Linear Statistical Models. Graybill FA, editor. New York: McGraw-Hill; 1961.
200. DeMets DL. Statistical issues in interpreting clinical trials. J Intern Med. 2004 May;255(5):529-37.
201. NICE technology appraisals [TA152]. National Institute for Health and Care Excellence; 2008 [updated 2008; cited 2015]; Available from: http://www.nice.org.uk/guidance/ta152.
202. Ribichini F, Tomai F, De Luca G, Boccuzzi G, Presbitero P, Pesarini G, et al. Immunosuppressive therapy with oral prednisone to prevent restenosis after PCI. A multicenter randomized trial. American Journal of Medicine. [Comparative Study
Multicenter Study
Randomized Controlled Trial
Research Support, Non-U.S. Gov't]. 2011 May;124(5):434-43.
203. Sardar P, Chatterjee S, Mukherjee D, Garratt KN. Steroids for the prevention of restenosis in bare-metal stents--a systematic review and meta-analysis. J Invasive Cardiol. 2012 Mar 2012;24(3):98-103.
204. Namdari M, Ghafarzadeh M, Nikoo MA. Efficacy of intramuscular methyl prednisolone in preventing restenosis after coronary artery stenting

with bare-metal stainless steel stent: a double-blind, randomised, controlled clinical trial. Cardiovascular Journal of Africa. 2009;22(2):67-9.
205. Ferrero V, Ribichini F, Rognoni A, Marino P, Brunelleschi S, Vassanelli C. Comparison of efficacy and safety of lower-dose to higher-dose oral prednisone after percutaneous coronary interventions (the IMPRESS-LD study). Am J Cardiol. 2007 Apr 15;99(8):1082-6.
206. Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. Circulation. 2003 Jan 28;107(3):363-9.
207. Vigushin DM, Pepys MB, Hawkins PN. Metabolic and scintigraphic studies of radioiodinated human C-reactive protein in health and disease. J Clin Invest. 1993 Apr;91(4):1351-7.
208. Abreu Filho LM, Forte AA, Sumita MK, Favarato D, Meireles GC, Abreu Filho LMd, et al. Influence of metal alloy and the profile of coronary stents in patients with multivessel coronary disease. Clinics (Sao Paulo, Brazil). [Comparative Study
Randomized Controlled Trial]. 2011;66(6):985-9.
209. Milewski K, Zurakowski A, Pajak J, Pajak-Zielinska E, Liszka L, Buszman PP, et al. Comparison of thin-strut cobalt-chromium stents and stainless steel stents in a porcine model of neointimal hyperplasia. Medical Science Monitor. [Comparative Study
Research Support, Non-U.S. Gov't]. 2010 Jan;16(1):BR40-4.
210. NICE technology appraisals [TA152] National Institute for Health and Care Excellence; 2008 [updated 2008 Feb 2014; cited 2014]; Available from: https://www.nice.org.uk/guidance/ta152.
211. Stone GW, Moses JW, Ellis SG, Schofer J, Dawkins KD, Morice MC, et al. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. N Engl J Med. 2007 Mar 8;356(10):998-1008.
212. Kastrati A, Mehilli J, Pache J, Kaiser C, Valgimigli M, Kelbaek H, et al. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med. 2007 Mar 8;356(10):1030-9.
213. Mauri L, Hsieh WH, Massaro JM, Ho KK, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. N Engl J Med. 2007 Mar 8;356(10):1020-9.

214. Spaulding C, Daemen J, Boersma E, Cutlip DE, Serruys PW. A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med. 2007 Mar 8;356(10):989-97.
215. Daemen J, Wenaweser P, Tsuchida K, Abrecht L, Vaina S, Morger C, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet. 2007 Feb 24;369(9562):667-78.
216. van der Giessen WJ, Lincoff AM, Schwartz RS, van Beusekom HM, Serruys PW, Holmes DR, Jr., et al. Marked inflammatory sequelae to implantation of biodegradable and nonbiodegradable polymers in porcine coronary arteries. Circulation. 1996 Oct 1;94(7):1690-7.
217. Joner M, Nakazawa G, Finn AV, Quee SC, Coleman L, Acampado E, et al. Endothelial cell recovery between comparator polymer-based drug-eluting stents. J Am Coll Cardiol. 2008 Jul 29;52(5):333-42.
218. Nebeker JR, Virmani R, Bennett CL, Hoffman JM, Samore MH, Alvarez J, et al. Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the Research on Adverse Drug Events and Reports (RADAR) project. J Am Coll Cardiol. 2006 Jan 3;47(1):175-81.
219. Virmani R, Liistro F, Stankovic G, Di Mario C, Montorfano M, Farb A, et al. Mechanism of late in-stent restenosis after implantation of a paclitaxel derivate-eluting polymer stent system in humans. Circulation. 2002 Nov 19;106(21):2649-51.
220. Garg S, Serruys PW. Coronary stents: current status. J Am Coll Cardiol. 2010 Aug 31;56(10 Suppl):S1-42.
221. Kandzari DE, Leon MB, Popma JJ, Fitzgerald PJ, O'Shaughnessy C, Ball MW, et al. Comparison of zotarolimus-eluting and sirolimus-eluting stents in patients with native coronary artery disease: a randomized controlled trial. J Am Coll Cardiol. 2006 Dec 19;48(12):2440-7.
222. Kandzari DE, Mauri L, Popma JJ, Turco MA, Gurbel PA, Fitzgerald PJ, et al. Late-term clinical outcomes with zotarolimus- and sirolimus-eluting stents. 5-year follow-up of the ENDEAVOR III (A Randomized Controlled Trial of the Medtronic Endeavor Drug [ABT-578] Eluting Coronary Stent System Versus the Cypher Sirolimus-Eluting Coronary Stent System in De Novo

Native Coronary Artery Lesions). JACC Cardiovasc Interv. 2011 May;4(5):543-50.
223. Leon MB, Mauri L, Popma JJ, Cutlip DE, Nikolsky E, O'Shaughnessy C, et al. A randomized comparison of the Endeavor zotarolimus-eluting stent versus the TAXUS paclitaxel-eluting stent in de novo native coronary lesions 12-month outcomes from the ENDEAVOR IV trial. J Am Coll Cardiol. 2010 Feb 9;55(6):543-54.
224. Kirtane AJ, Leon MB, Ball MW, Bajwa HS, Sketch MH, Jr., Coleman PS, et al. The "final" 5-year follow-up from the ENDEAVOR IV trial comparing a zotarolimus-eluting stent with a paclitaxel-eluting stent. JACC Cardiovasc Interv. 2013 Apr;6(4):325-33.
225. Serruys PW, Ruygrok P, Neuzner J, Piek JJ, Seth A, Schofer JJ, et al. A randomised comparison of an everolimus-eluting coronary stent with a paclitaxel-eluting coronary stent:the SPIRIT II trial. EuroIntervention. 2006 Nov;2(3):286-94.
226. Stone GW, Midei M, Newman W, Sanz M, Hermiller JB, Williams J, et al. Comparison of an everolimus-eluting stent and a paclitaxel-eluting stent in patients with coronary artery disease: a randomized trial. JAMA. 2008 Apr 23;299(16):1903-13.
227. Gada H, Kirtane AJ, Newman W, Sanz M, Hermiller JB, Mahaffey KW, et al. 5-year results of a randomized comparison of XIENCE V everolimus-eluting and TAXUS paclitaxel-eluting stents: final results from the SPIRIT III trial (clinical evaluation of the XIENCE V everolimus eluting coronary stent system in the treatment of patients with de novo native coronary artery lesions). JACC Cardiovasc Interv. 2013 Dec;6(12):1263-6.
228. Stone GW, Rizvi A, Newman W, Mastali K, Wang JC, Caputo R, et al. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. N Engl J Med. 2010 May 6;362(18):1663-74.
229. Kedhi E, Joesoef KS, McFadden E, Wassing J, van Mieghem C, Goedhart D, et al. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. Lancet. 2010 Jan 16;375(9710):201-9.

230. Alazzoni A, Al-Saleh A, Jolly SS. Everolimus-Eluting versus Paclitaxel-Eluting Stents in Percutaneous Coronary Intervention: Meta-Analysis of Randomized Trials. Thrombosis. 2012;2012:126369.
231. Jensen LO, Thayssen P, Hansen HS, Christiansen EH, Tilsted HH, Krusell LR, et al. Randomized comparison of everolimus-eluting and sirolimus-eluting stents in patients treated with percutaneous coronary intervention: the Scandinavian Organization for Randomized Trials with Clinical Outcome IV (SORT OUT IV). Circulation. 2012 Mar 13;125(10):1246-55.
232. Jensen LO, Thayssen P, Maeng M, Christiansen EH, Ravkilde J, Hansen KN, et al. Three-year outcomes after revascularization with everolimus- and sirolimus-eluting stents from the SORT OUT IV trial. JACC Cardiovasc Interv. 2014 Aug;7(8):840-8.
233. de Waha A, Dibra A, Byrne RA, Ndrepepa G, Mehilli J, Fusaro M, et al. Everolimus-eluting versus sirolimus-eluting stents: a meta-analysis of randomized trials. Circ Cardiovasc Interv. 2011 Aug;4(4):371-7.
234. Farb A, John M, Acampado E, Kolodgie FD, Prescott MF, Virmani R. Oral everolimus inhibits in-stent neointimal growth. Circulation. 2002 Oct 29;106(18):2379-84.
235. Heldman AW, Cheng L, Jenkins GM, Heller PF, Kim DW, Ware M, Jr., et al. Paclitaxel stent coating inhibits neointimal hyperplasia at 4 weeks in a porcine model of coronary restenosis. Circulation. 2001 May 8;103(18):2289-95.
236. Camenzind E, Wijns W, Mauri L, Kurowski V, Parikh K, Gao R, et al. Stent thrombosis and major clinical events at 3 years after zotarolimus-eluting or sirolimus-eluting coronary stent implantation: a randomised, multicentre, open-label, controlled trial. Lancet. 2012 Oct 20;380(9851):1396-405.
237. Wijns W, Steg PG, Mauri L, Kurowski V, Parikh K, Gao R, et al. Endeavour zotarolimus-eluting stent reduces stent thrombosis and improves clinical outcomes compared with cypher sirolimus-eluting stent: 4-year results of the PROTECT randomized trial. Eur Heart J. 2014 Oct 21;35(40):2812-20.
238. Camenzind E, editor. PROTECT: Final Five Year Results from the Randomized Drug Eluting Stent Trial PROTECT: the Patient Related

Outcomes wiTh Endeavor versus Cypher stenting Trial. European Society of Cardiology Congress; 2014; Barcelona, Spain.
239. Karalis I, Ahmed TA, Jukema JW. Late acquired stent malapposition: why, when and how to handle? Heart. 2012 Oct;98(20):1529-36.
240. Gwon HC, Hahn JY, Park KW, Song YB, Chae IH, Lim DS, et al. Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomized, multicenter study. Circulation. 2012 Jan 24;125(3):505-13.
241. Valgimigli M, Campo G, Monti M, Vranckx P, Percoco G, Tumscitz C, et al. Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. Circulation. 2012 Apr 24;125(16):2015-26.
242. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation. 2011 Jun 14;123(23):2736-47.
243. Valgimigli M, Borghesi M, Tebaldi M, Vranckx P, Parrinello G, Ferrari R. Should duration of dual antiplatelet therapy depend on the type and/or potency of implanted stent? A pre-specified analysis from the PROlonging Dual antiplatelet treatment after Grading stent-induced Intimal hyperplasia studY (PRODIGY). Eur Heart J. 2013 Mar;34(12):909-19.
244. Kim BK, Hong MK, Shin DH, Nam CM, Kim JS, Ko YG, et al. A new strategy for discontinuation of dual antiplatelet therapy: the RESET Trial (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation). J Am Coll Cardiol. 2012 Oct 9;60(15):1340-8.
245. Feres F, Costa RA, Abizaid A, Leon MB, Marin-Neto JA, Botelho RV, et al. Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: the OPTIMIZE randomized trial. JAMA. 2013 Dec 18;310(23):2510-22.
246. El-Hayek G, Messerli F, Bangalore S, Hong MK, Herzog E, Benjo A, et al. Meta-analysis of randomized clinical trials comparing short-term versus

long-term dual antiplatelet therapy following drug-eluting stents. Am J Cardiol. 2014 Jul 15;114(2):236-42.
247. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med. 2014 Dec 4;371(23):2155-66.
248. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. The GUSTO investigators. N Engl J Med. 1993 Sep 2;329(10):673-82.
249. Park SJ, Park DW, Kim YH, Kang SJ, Lee SW, Lee CW, et al. Duration of dual antiplatelet therapy after implantation of drug-eluting stents. N Engl J Med. 2010 Apr 15;362(15):1374-82.
250. Collet J-P, Silvain J, Barthelemy O, Range G, Cayla G, Van Belle E, et al. Dual-antiplatelet treatment beyond 1 year after drug-eluting stent implantation (ARCTIC-Interruption): a randomised trial. The Lancet. 2014 2015/04/07;384(9954):1577-85.
251. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J. 2014 Oct 1;35(37):2541-619.
252. Meredith IT, Worthley S, Whitbourn R, Walters D, Popma J, Cutlip D, et al. The next-generation Endeavor Resolute stent: 4-month clinical and angiographic results from the Endeavor Resolute first-in-man trial. EuroIntervention. 2007 May;3(1):50-3.
253. Meredith IT, Worthley S, Whitbourn R, Walters DL, McClean D, Horrigan M, et al. Clinical and angiographic results with the next-generation resolute stent system: a prospective, multicenter, first-in-human trial. JACC Cardiovasc Interv. 2009 Oct;2(10):977-85.
254. von Birgelen C, Basalus MWZ, Tandjung K, van Houwelingen KG, Stoel MG, Louwerenburg JW, et al. A Randomized Controlled Trial in Second-Generation Zotarolimus-Eluting Resolute Stents Versus Everolimus-Eluting

Xience V Stents in Real-World Patients: The TWENTE Trial. Journal of the American College of Cardiology. 2012;59(15):1350-61.
255. Stone GW, Teirstein PS, Meredith IT, Farah B, Dubois CL, Feldman RL, et al. A prospective, randomized evaluation of a novel everolimus-eluting coronary stent: the PLATINUM (a Prospective, Randomized, Multicenter Trial to Assess an Everolimus-Eluting Coronary Stent System [PROMUS Element] for the Treatment of Up to Two de Novo Coronary Artery Lesions) trial. J Am Coll Cardiol. 2011 Apr 19;57(16):1700-8.
256. Windecker S, Serruys PW, Wandel S, Buszman P, Trznadel S, Linke A, et al. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. Lancet. 2008 Sep 27;372(9644):1163-73.
257. Serruys PW, Farooq V, Kalesan B, de Vries T, Buszman P, Linke A, et al. Improved safety and reduction in stent thrombosis associated with biodegradable polymer-based biolimus-eluting stents versus durable polymer-based sirolimus-eluting stents in patients with coronary artery disease: final 5-year report of the LEADERS (Limus Eluted From A Durable Versus ERodable Stent Coating) randomized, noninferiority trial. JACC Cardiovasc Interv. 2013 Aug;6(8):777-89.
258. Christiansen EH, Jensen LO, Thayssen P, Tilsted HH, Krusell LR, Hansen KN, et al. Biolimus-eluting biodegradable polymer-coated stent versus durable polymer-coated sirolimus-eluting stent in unselected patients receiving percutaneous coronary intervention (SORT OUT V): a randomised non-inferiority trial. Lancet. 2013 Feb 23;381(9867):661-9.
259. Smits PC, Hofma S, Togni M, Vazquez N, Valdes M, Voudris V, et al. Abluminal biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent (COMPARE II): a randomised, controlled, non-inferiority trial. Lancet. 2013 Feb 23;381(9867):651-60.
260. Meredith IT, Verheye S, Dubois CL, Dens J, Fajadet J, Carrie D, et al. Primary endpoint results of the EVOLVE trial: a randomized evaluation of a novel bioabsorbable polymer-coated, everolimus-eluting coronary stent. J Am Coll Cardiol. 2012 Apr 10;59(15):1362-70.
261. Meredith IT, Verheye S, Weissman NJ, Barragan P, Scott D, Valdes Chavarri M, et al. Six-month IVUS and two-year clinical outcomes in the

EVOLVE FHU trial: a randomised evaluation of a novel bioabsorbable polymer-coated, everolimus-eluting stent. EuroIntervention. 2013 Jul;9(3):308-15.
262. Ormiston JA, Serruys PW. Bioabsorbable coronary stents. Circ Cardiovasc Interv. 2009 Jun;2(3):255-60.
263. Ormiston JA, Webster MW, Armstrong G. First-in-human implantation of a fully bioabsorbable drug-eluting stent: the BVS poly-L-lactic acid everolimus-eluting coronary stent. Catheter Cardiovasc Interv. 2007 Jan;69(1):128-31.
264. Serruys PW, Chevalier B, Dudek D, Cequier A, Carrie D, Iniguez A, et al. A bioresorbable everolimus-eluting scaffold versus a metallic everolimus-eluting stent for ischaemic heart disease caused by de-novo native coronary artery lesions (ABSORB II): an interim 1-year analysis of clinical and procedural secondary outcomes from a randomised controlled trial. Lancet. 2015 Jan 3;385(9962):43-54.
265. Puricel S, Arroyo D, Corpataux N, Baeriswyl G, Lehmann S, Kallinikou Z, et al. Comparison of everolimus- and biolimus-eluting coronary stents with everolimus-eluting bioresorbable vascular scaffolds. J Am Coll Cardiol. 2015 Mar 3;65(8):791-801.
266. Kimura T, Kozuma K, Tanabe K, Nakamura S, Yamane M, Muramatsu T, et al. A randomized trial evaluating everolimus-eluting Absorb bioresorbable scaffolds vs. everolimus-eluting metallic stents in patients with coronary artery disease: ABSORB Japan. Eur Heart J. 2015 Dec 14;36(47):3332-42.
267. Ellis SG, Kereiakes DJ, Metzger DC, Caputo RP, Rizik DG, Teirstein PS, et al. Everolimus-Eluting Bioresorbable Scaffolds for Coronary Artery Disease. N Engl J Med. 2015 Nov 12;373(20):1905-15.
268. Gao R, Yang Y, Han Y, Huo Y, Chen J, Yu B, et al. Bioresorbable Vascular Scaffolds Versus Metallic Stents in Patients With Coronary Artery Disease: ABSORB China Trial. J Am Coll Cardiol. 2015 Dec 1;66(21):2298-309.
269. Sabate M, Windecker S, Iniguez A, Okkels-Jensen L, Cequier A, Brugaletta S, et al. Everolimus-eluting bioresorbable stent vs. durable polymer everolimus-eluting metallic stent in patients with ST-segment elevation

myocardial infarction: results of the randomized ABSORB ST-segment elevation myocardial infarction-TROFI II trial. Eur Heart J. 2016 Jan 14;37(3):229-40.
270. Cassese S, Byrne RA, Ndrepepa G, Kufner S, Wiebe J, Repp J, et al. Everolimus-eluting bioresorbable vascular scaffolds versus everolimus-eluting metallic stents: a meta-analysis of randomised controlled trials. Lancet. 2016 Feb 6;387(10018):537-44.

Appendix

Publication of main study findings

International Journal of Cardiology 216 (2016) 1–8

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

The SSTARS (STeroids and Stents Against Re-Stenosis) Trial: Different stent alloys and the use of peri-procedural oral corticosteroids to prevent in-segment restenosis after percutaneous coronary intervention

Z. Adam [a,*,1], A. Turley [a,1], J.M. Mason [b,1], A.S. Kasim [c,1], D. Newby [d,1], N. Mills [d,1], G. Padfield [d,1], L. Thompson [a,1], R. Morley [a,1], J.A. Hall [a,1], R.A. Wright [a,1], D.F. Muir [a,1], A.G.C. Sutton [a,1], N. Swanson [a,1], J. Carter [a,1], R. Bilous [a,1], S. Jones [a,1], M.A. de Belder [a,1]

[a] The James Cook University Hospital, South Tees Hospitals NHS Trust, Marton Rd, Middlesbrough TS4 3BW, United Kingdom
[b] Warwick Medical School, University of Warwick, Coventry CV4 7AL, United Kingdom
[c] School of Medicine, Pharmacy and Health, Durham University, Queen's Campus, Wolfson Research Institute, University Boulevard, Stockton-on-Tees TS17 6BH, United Kingdom
[d] Royal Infirmary of Edinburgh, Lothian University Hospitals NHS Trust, Old Dalkeith Road, Edinburgh EH16 4SA, United Kingdom

ARTICLE INFO

Article history:
Received 24 March 2016
Accepted 11 April 2016
Available online xxxx

Keywords:
Restenosis
Prednisolone
Cobalt chromium
Stainless steel
Angioplasty

ABSTRACT

Background: Stent design and technological modifications to allow for anti-proliferative drug elution influence restenosis rates following percutaneous coronary intervention (PCI). We aimed to investigate whether peri-procedural administration of corticosteroids or the use of thinner strut cobalt alloy stents would reduce rates of binary angiographic restenosis (BAR) after PCI.

Methods: This was a two centre, mixed single and double blinded, randomised controlled trial using a factorial design. We compared (a) the use of prednisolone to placebo, starting at least six hours pre-PCI and continued for 28 days post-PCI, and (b) cobalt chromium (CoCr) to stainless steel (SS) alloy stents, in patients admitted for PCI. The primary end-point was BAR at six months.

Results: 315 patients (359 lesions) were randomly assigned to either placebo (n = 145) or prednisolone (n = 170) and SS (n = 160) or CoCr (n = 160). The majority (58%) presented with an ACS, 11% had diabetes and 287 (91%) completed angiographic follow up. BAR occurred in 26 cases in the placebo group (19.7%) versus 31 cases in the prednisolone group (20.0%) respectively, p = 1.00. For the comparison between SS and CoCr stents, BAR occurred in 32 patients (21.6%) versus 25 patients (18.0%) respectively, p = 0.46.

Conclusion: Our study showed that treating patients with a moderately high dose of prednisolone for 28 days following PCI with BMS did not reduce the incidence of BAR. In addition, we showed no significant reduction in 6 month restenosis rates with stents composed of CoCr alloy compared to SS (http://www.isrctn.com/ISRCTN05886349).

1. Introduction

Inflammation is one of the key mechanisms of restenosis after intra-coronary stent implantation [1]. An inflammatory cascade results in neo-intimal proliferation which, if excessive, results in restenosis. Drug eluting stents (DES), offering local delivery of immunosuppressive or anti-inflammatory drugs[2], have been the most successful means of reducing the need for target vessel revascularisation compared with bare metal stents (BMS) [2]. Despite the introduction of DES, BMS are still used in patients at low risk of restenosis and in patients for whom a short course of dual anti-platelet drug therapy is desirable(e.g. when there are concerns about risk of bleeding). DES are also more costly and so BMS may also be favoured for economic reasons in some health economies. There have also been concerns about stent thrombosis and accelerated neoatherosclerosis, particularly with first generation DES [3–5].

Issues for DES include drug delivery and polymer coatings (which themselves are associated with an inflammatory response). An alternative approach using systemic anti-inflammatory agents has also been tried. Corticosteroids mediate their effects primarily through the modulation of the cytosolic glucocorticoid receptor. Expression of anti-inflammatory proteins is upregulated and expression of pro-inflammatory proteins repressed [6,7], both of which may reduce restenosis.

The pathology of restenosis in BMS begins early after PCI and inflammatory reaction within the first 30 days is important [1]. Thus, both the

* Corresponding author at: The James Cook University Hospital, Marton Road, Middlesbrough TS4 3BW, United Kingdom.
E-mail address: zulfiquar.adam@nhs.net (Z. Adam).
[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

http://dx.doi.org/10.1016/j.ijcard.2016.04.105
0167-5273/

timing and duration of corticosteroid therapy may be relevant to lowering restenosis rates and it may be important to suppress the inflammatory response prior to stent implantation. Corticosteroids have been studied in different contexts, including balloon angioplasty with and without stenting, and with variable duration of treatment both pre-procedure or post procedure. Results have been mixed [8–10].

Another important factor influencing restenosis in BMS is strut thickness. In stainless steel (SS) stents, restenosis occurs less frequently with thinner struts [11,12]. These findings have influenced the drive towards the use of higher radial strength materials such as cobalt chromium (CoCr) alloys that allow reduction in strut thickness. Early registry studies supported this concept reporting restenosis in 15.7% of patients with cobalt alloys [13,14] but there has been a lack of randomised data.

This trial investigated whether administration of corticosteroids (started several hours prior to PCI) or the use of CoCr stents would reduce the rate of binary angiographic restenosis (BAR) after PCI.

2. Methods

2.1. Study design

Using a 2 × 2 factorial design, a two centre, randomised controlled trial compared the use of prednisolone to placebo and CoCr to SS steel alloy stents in patients admitted for PCI.

The trial featured a mixed single and double blinded randomised controlled design. Both the patients and the physicians performing PCI were blind to the prednisolone/placebo allocation but only the patients were blinded to the stent allocation. Patients were block randomised to prednisolone or placebo prior to angiography and subsequently to CoCr or SS stent once eligibility was confirmed. To provide a loading dose of prednisolone prior to the procedure, randomisation to prednisolone or placebo occurred in a 1:1 ratio prior to PCI. Patients eligible were randomised to either a CoCr or SS stent in a 1:1 ratio. Allocation of patients into intervention groups was achieved using a closed envelope system, managed by a research team working independently of the clinical team.

The primary objective was to show that prednisolone (compared with placebo) or CoCr stents (compared with SS stents) reduced 6 month BAR, defined within the stented segment plus 5 mm proximal and distal to this. Secondary objectives included investigation of the effects of the interventions on a number of pre-specified angiographic measures (see below), impact of highly sensitive (hs)-CRP, and assessment of patient safety. Major adverse cardiovascular and cerebrovascular events (MACCE: death, myocardial infarction, cerebrovascular event and target vessel revascularisation) were also recorded.

2.2. Setting

The study was performed in two tertiary cardiac units in the United Kingdom, The James Cook University Hospital in Middlesbrough and the Royal Infirmary of Edinburgh.

2.3. Recruitment

Patients eligible for the study were identified from the elective waiting list or were awaiting angiography after an acute coronary syndrome (ACS). Inclusion criteria for the double randomisation were: awaiting PCI for symptomatic coronary artery disease (elective or acute); documented myocardial ischaemia; coronary angiography demonstrating at least a 50% reduction of the luminal diameter (by visual estimate) in at least one native coronary artery; any lesion for which the operator (consultant interventional cardiologist) assessed a non-drug eluting stent was appropriate. Exclusion criteria included proposed use of a drug eluting stent in the study lesion(s); left main stem stenosis ≥50%; primary PCI for ST elevation myocardial infarction; corticosteroid therapy for an alternative reason within 30 days of study enrolment; contraindication to corticosteroid use; previous recruitment to the trial; non-cardiac disease likely to cause death within six months; out of region hospital transfers.

2.4. Trials procedures

Prednisolone 40 mg/day (or placebo) was started at least 6 h pre-procedure and continued for 14 days, stepped down to 20 mg/day from days 15–21 and 10 mg/day from days 22–28.

Patients were pre-treated with clopidogrel. Coronary angiography was performed via femoral or radial artery puncture. After sheath insertion, a bolus of heparin was administered (dose: weight related with a minimum of 70 μ/kg). Before angiography, 200 μg of intracoronary nitrate was administered. Lesions in large vessels (visual estimate of ≥3 mm) were treated according to randomisation between the Multilink Zeta™ (SS) and Multilink Vision™ (CoCr) stents (Abbott Vascular, USA). Additional lesions in small vessels could be treated with Cypher Select™ stents (Cordis, USA), eluting sirolimus but as the trial progressed other second generation DES were also employed. Patients could be enrolled into the trial with lesions in small vessels if the operator thought it was reasonable to treat with a BMS.

Due to dual oral antiplatelet therapy plus oral corticosteroid use, all patients received empirical proton pump inhibitor cover (lansoprazole 30 mg/day for 28-days) for the duration of the prednisolone course. Optimal medical therapy with beta-blockers, angiotensin-converting enzyme inhibitors and statins was encouraged; use of other agents was at the discretion of the attending physician. Patients were treated with aspirin 75 mg daily indefinitely and clopidogrel 75 mg daily for a minimum of four weeks.

All patients randomised were routinely brought back for repeat angiography. Quantitative coronary angiography (QCA) was performed as at the outset for all treated segments.

Angiographic measurements were made before predilatation (baseline), after the stenting procedure and at follow up using the Philips Inturis™ system by a research fellow (ZA) who performed the analysis independent of the clinical information. Measurements were made in diastole and performed in two orthogonal views. The contrast filled guiding or diagnostic catheter was used for magnification calibration. QCA measures included: minimal luminal diameter (MLD); reference diameter, derived as either an average of the proximal and distal reference diameters or the interpolated diameter derived by the software for the selected segment; percent diameter stenosis; in-stent restenosis, defined as ≥50% diameter stenosis within the stent at follow up; in-segment restenosis, defined as ≥50% stenosis within the stented segment or within 5 mm proximal or distal to the stent edges; acute gain, defined as the difference between MLD after stent implantation and the MLD before PCI; late loss, defined as the difference between the MLD after stent insertion and the MLD at follow up; net gain, defined as the difference between acute gain and late loss.

2.5. Biomarkers and monitoring of blood glucose

Hs-CRP and glycated haemoglobin (HbA1c) were measured at five time-points: at study entry, on the day of the procedure, at seven days, at 30 days and finally at six month follow-up. Due to the potential problem of hyperglycaemia in patients randomised to corticosteroid treatment, all patients were given home glucose monitoring kits. Prior to hospital discharge they were instructed on the correct use of home monitoring. They were also educated on normal values and provided with contact details of the research team, in hours, or cardiology on call team, out of hours, for support and advice if their blood glucose recordings were high.

2.6. Safety

All patients were monitored for bleeding or for hyperglycaemia. Bleeding episodes were classified according to the Thrombolysis in Myocardial Infarction (TIMI) study group criteria for bleeding [15]. Adverse events were recorded according to expectedness and relatedness.

2.7. Statistical analysis

The sample size for a 2×2 factorial design was calculated to detect an absolute difference in in-segment restenosis rates for both the stent and drug comparisons from 30% to 15%, assuming 5% alpha, 80% power and 15% loss to follow-up, indicating 137 patients per group (548 in total), and assuming no interaction between comparison groups. The planned sample size was not achieved and 315 patients were recruited within the constraints of unplanned complexities for patient identification and recruitment. The power calculation for the study was revisited prospectively before analysis of trial data and informed by recent evidence. Assuming restenosis occurred in 30% of patients, and that both chromium cobalt stenting and prednisolone might halve the risk of restenosis, the average 'intervention rate' would be 11.25% and the average 'control' would be 22.5% within each comparison group. Assuming alpha of 5%, the trial had 72% power to detect an absolute difference of 11.25% between groups, using a two-sided test (nQuery + nTerim 2.0).

Analysis was performed by the principle of intention to treat (ITT), with analyses conducted according to assignment at randomisation [16,17]. The intention to treat principle allows for modification due to missing data, for which there is no completely satisfactory remedy since strong assumptions are required regardless of the approach taken [18,19]. Primary inference was based on the primary endpoint analysis as a difference in proportions, using Fisher's exact test [20] with statistical significance at the 5% level (2-sided), for combined stent groups and drug groups. Analyses of all secondary endpoints and adjusted analyses were considered supportive to the primary analysis so no adjustments for multiple comparisons were made.

Sensitivity analysis of the primary endpoint was performed at the level of the patient and lesion using generalised linear models (GLMs) with separate indicator variables for steroid and stent groups as well as their interactions. Secondary analyses explored changes in angiographic measures using GLMs [19,21] and the role of covariates such as CRP level.

Patient demographics and study endpoints involving categorical variables were estimated using Fisher's exact test; continuous measures were evaluated using Student's t-test where appropriate, otherwise suitable non-parametric tests were used.

2.8. Ethics and governance

The conduct of the trial was subject to local site and London Multicentre Research Ethics Committee (MREC) approvals (ref: 04/MREC2/061) and registered with UK Trials (ISRCTN 05886349).

3. Results

Between January 2006 and May 2012, 315 patients were recruited and 359 lesions treated. The trial initially recruited mainly elective patients in whom angiographic status was known but over the course of the trial most patients underwent PCI immediately following angiography. In addition, a rapid increase in the use of DES made recruitment a challenge (see consort diagram, Fig. 1). The mean age was 60 years (range 37 to 87 years), 85% were male, 42% were elective PCI cases and the mean number of lesions treated was 1.14 (range 1 to 4). Groups were similar at baseline, with no significant baseline differences (Table 1). Of 315 patients, 308 (98%) received the treatment allocated to them and there were no instances of treatment cross-over.

3.1. Angiographic measures

These are shown for primary target lesions in Table 2. There was no difference in stenosis by any measure pre or post PCI, or at follow-up. This was also the case when the data were analysed using the interpolated reference diameter. Across all groups, average in-segment diameter stenosis was: 70.3% (95% CI: 68.8% to 71.7%) pre-PCI; 6.6% (95% CI: 5.9% to 7.3%) immediately post-PCI; and 35.2% (95% CI: 33.3% to 37.0%) at final follow up. Acute gain was 2.07 mm (95% CI: 2.02 to 2.13 mm), late loss 1.04 mm (95% CI: −0.98 to 1.10 mm) and net gain was 1.04 (95% CI: −0.97 to 1.12 mm). The results were qualitatively the same for all lesions. The cumulative distribution of stenosis in target lesions is shown in Fig. 2.

3.2. Endpoints

The primary endpoint of binary angiographic restenosis is reported in Table 3. There was no difference in restenosis between treatment groups. In-segment average restenosis across all groups was 19.1% (95% CI: 14.7% to 24.2%). However there was significant variation within the individual treatment combinations (varying from 11.7% to 26.4%) and a significant interaction was identified within a general-linear model. For in-stent average restenosis of target lesions the log-odds findings (x) were:

$$x = \underset{p<0.001}{-2.024} + \underset{p=0.096}{0.804}.drug + \underset{p=0.039}{0.999}.stent \underset{p=0.015}{-1.555}.drug \cdot stent$$

where *drug* is an indicator variable for prednisolone, *stent* is an indicator for stainless steel stent and *drug.stent* is the interaction term for *stent* and *drug* combined. Findings were qualitatively similar, regardless of the restenosis definition taken for target lesions or use of hierarchical models including all treated lesions. Analysis of stenosis percentage (y) using a general linear model did not find an interaction.

$$y = \underset{p<0.001}{33.40} + \underset{p=0.26}{3.11}.drug + \underset{p=0.25}{3.20}.stent \underset{p=0.12.}{-5.82}.drug \cdot stent$$

Findings were qualitatively similar, regardless of the restenosis definition taken for target lesions or use of hierarchical models including all treated lesions. The explanation for these findings is apparent in the comparison of cumulative stenosis rates comparing the treatment combinations (see Fig. 2). Although there is no apparent difference over much of the distribution, there are apparent differences in the tail at the 50% stenosis point. Thus the finding may be an artefact of selectively dichotomising a continuous outcome and may not be of clinical importance.

There were no important differences in any other study endpoints, adverse or serious adverse events (Table 3).

3.3. Bleeding

Use of prednisolone did not influence the frequency of bleeding episodes: 7.6% vs. 5.5% for placebo, $p = 0.50$). Almost all bleeds were minor and mainly related to femoral access (2.9% vs. 2.8% for placebo) at the time of the procedure. There was only one major bleeding episode (per rectum bleeding requiring transfusion). This occurred in the placebo group during the index admission and study medication was stopped.

3.4. Biomarkers and hyperglycaemia (Table 4)

Hs-CRP measurements were not available for 16 patients. The pre-PCI hs-CRP measurement was ≤5 mg/L in 213 patients (71%) of whom only 28 (13%) had a raised CRP at day 7. Use of prednisolone was associated with a suppression of hs-CRP response at day 7 (−5.98 mg/L, 95%

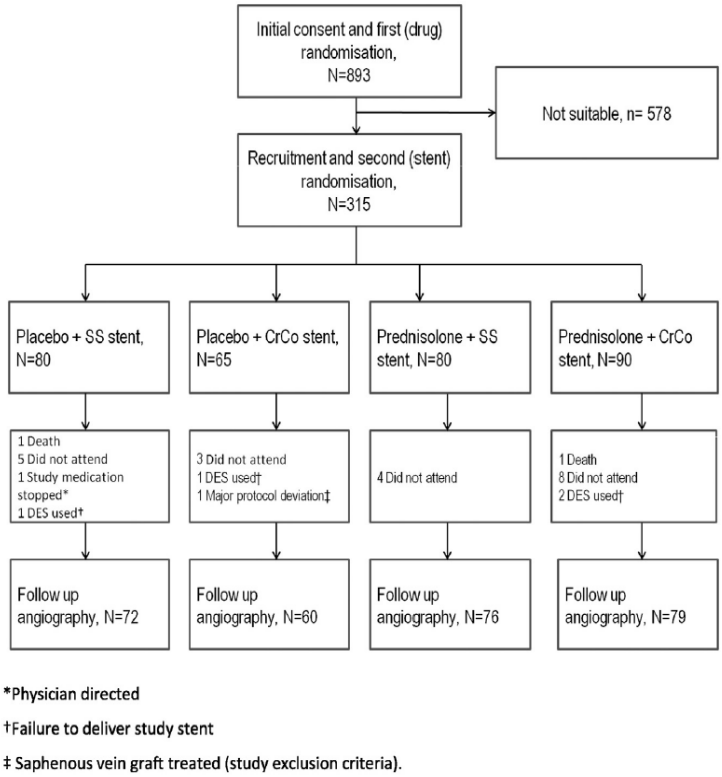


Fig. 1. Consort diagram.

CI: −8.35 to −3.61, p < 0.001) with a small rebound at day 30 (2.71 mg/L, 95% CI: 0.78 to 4.65, p = 0.006). There was no evidence of longer term changes at six months. There was no correlation between lowering hs-CRP and stenosis diameter at follow-up.

More patients had home blood glucose levels greater than 11 mmol/L in the prednisolone than placebo group during follow-up: 22.9% vs. 6.9% respectively (p < 0.001). This finding was apparent qualitatively in diabetic patients: 55.0% vs. 28.6% (p = 0.17), as well as in non-diabetic patients: 18.7% vs. 4.6% respectively (p < 0.001). In the majority of cases, dietary advice and reassurance were sufficient and there was no significant difference between the groups in use of additional oral hypoglycaemic therapy, insulin or need for study medication to be stopped. Glycated haemoglobin (Hb_{A1c}) was also monitored at five points during the trial. There were no clinically important differences between treatments during the trial.

4. Discussion

This trial was designed to address two separate questions. Was there was any benefit of (a) pre-procedural systemic corticosteroid therapy and (b) the use of thinner strut cobalt alloy stents in preventing BAR after BMS implantation? At the time of trial conception, both were seen as promising especially as there was concern about longer term safety with DES [4]. We found no benefit from the use of 28-days of prednisolone started at least 6 h pre-procedurally or from the use of cobalt chromium stents.

Compared with previous randomised studies [9,10] of corticosteroids, one of the key differences in design of this trial was the use of pre-procedural steroids and duration of treatment for 28 days. In the study by Lee et al., a single pulsed dose of intravenous methylprednisolone pre-procedure did not confer any benefit in reducing restenosis in BMS [9]. In The Immunosuppressive Therapy for the Prevention of Restenosis after Coronary Artery Stent Implantation (IMPRESS) study, prednisone administered 72 h post procedure for 45 days in patients with elevated post-procedural CRP levels but normal pre-procedural CRP levels resulted in marked reductions in restenosis [10] with benefit extending clinically to five years [22]. There was only a small proportion (n = 28/213) of such patients in our study, although our post procedure hs-CRP levels were measured at day 7. Our steroid protocol was designed to ensure therapeutic levels of anti-inflammatory activity before the initial injury from stenting as well as the resultant inflammation. Notably, we did not see any association between reducing hs-CRP and lowering restenosis. Our findings suggest that only a minority of elective and urgent patients fulfil the requirements of the IMPRESS protocol. Moreover, in routine clinical practice, the choice of stent at the time of the procedure cannot be determined by what the hs-CRP might be a few days later. Even in patients treated with BMS, the logistics of arranging for a routine hs-CRP measurement at 72 h and then determining the use of steroids is difficult.

Our findings also differ from the most recent meta-analysis of five studies investigating the role of corticosteroids in reducing restenosis rates [23]. Separate analyses were performed for two trials involving balloon angioplasty alone [8,24] and three involving BMS implantation [9,10,25]. Corticosteroids did reduce restenosis following BMS implantation (RR 0.60, 95% CI 0.37–0.97). Two of these trials, the study by Lee et al. and IMPRESS have been discussed above. In the Cortisone plus BMS or DES alone to Eliminate Restenosis (CEREA-DES) trial, the study endpoint was not angiographic restenosis but rather a combined clinical endpoint of major adverse cardiovascular events (MACE). In about half of these patients CRP was raised post PCI, defined as >3 mg/L, and there was a significant reduction in MACE (23% vs. 8% for prednisone treated, p = 0.03) but it is not clear whether this was driven by less restenosis; target lesion revascularisation was 12% vs.

Table 1
Baseline patient characteristics.

	Placebo, N = 145				Prednisolone, N = 170				Drug p	Stent p
	CoCr, n = 65		SS, n = 80		CoCr, n = 90		SS, n = 80			
Actual treatment	64	(98.5%)	79	(98.8%)	87	(96.7%)	78	(97.5%)		
Elective PCI	26	(40.0%)	35	(43.8%)	37	(41.1%)	34	(42.5%)	1.00	0.73
Male	56	(86.2%)	68	(85.0%)	74	(82.2%)	71	(88.8%)	1.00	0.52
Age, y	60.2	(9.6)	60.0	(8.5)	59.5	(10.3)	62.2	(9.7)	0.54	0.23
Height, m	1.73	(0.08)	1.74	(0.09)	1.73	(0.09)	1.74	(0.08)	0.89	0.38
Weight, kg	85.5	(17.6)	87.5	(15.4)	88.9	(18.8)	86.7	(14.7)	0.50	0.82
Smoking status									0.67	0.53
Never smoked	22	(33.8%)	30	(37.5%)	33	(36.7%)	24	(30.0%)		
Ex-smoker	19	(29.2%)	30	(37.5%)	33	(36.7%)	33	(41.3%)		
Current smoker	24	(36.9%)	20	(25.0%)	24	(26.7%)	23	(28.8%)		
History of hypertension	35	(53.8%)	42	(52.5%)	50	(55.6%)	35	(43.8%)	0.65	0.26
Family history of IHD	40	(61.5%)	42	(52.5%)	50	(55.6%)	45	(56.3%)	0.91	0.57
Previous MI	9	(13.8%)	10	(12.5%)	8	(8.9%)	12	(15.0%)	0.73	0.50
Previous CABG	3	(4.6%)	0	(0.0%)	1	(1.1%)	1	(1.3%)	0.67	0.21
Previous PCI	0	(0.0%)	3	(3.8%)	5	(5.6%)	7	(8.8%)	0.06	0.29
Previous TIA/CVA	1	(1.5%)	1	(1.3%)	3	(3.3%)	4	(5.0%)	0.19	1.00
History of peripheral VD	1	(1.5%)	4	(5.0%)	4	(4.4%)	0	(0.0%)	0.74	0.75
History of LVSD	2	(3.1%)	7	(8.8%)	3	(3.3%)	5	(6.3%)	0.62	0.13
Renal disease	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	-	-
Diabetes (I or II)	6	(9.2%)	8	(10.0%)	13	(14.4%)	7	(8.8%)	0.59	0.47
Insulin diabetic	1	(1.5%)	2	(2.5%)	2	(2.2%)	0	(0.0%)	0.67	0.68
HbA1c, %	5.75	(0.85)	5.86	(0.97)	5.83	(0.87)	5.71	(0.50)	0.75	0.88
Hypercholesterolaemia	61	(93.8%)	72	(90.0%)	76	(84.4%)	70	(87.5%)	0.11	1.00
Cholesterol, mmol/L	4.9	(1.1)	4.6	(1.3)	4.8	(1.3)	4.5	(1.0)	0.46	0.04
Creatinine value, μmol/L	91.1	(17.4)	94.0	(18.8)	90.5	(20.3)	93.4	(15.5)	0.67	0.15
Troponin, μg/L	1.35	(4.65)	4.63	(11.54)	1.39	(2.75)	1.98	(5.52)	0.17	0.07
CRP, mg/L	6.31	(14.53)	8.32	(13.11)	5.39	(11.77)	6.36	(15.07)	0.35	0.35
Number of lesions									0.46	0.72
1	59	(90.8%)	71	(88.8%)	77	(85.6%)	69	(86.3%)		
2	4	(6.2%)	9	(11.3%)	12	(13.3%)	10	(12.5%)		
3	1	(1.5%)	0	(0.0%)	1	(1.1%)	1	(1.3%)		
4	1	(1.5%)	0	(0.0%)	0	(0.0%)	0	(0.0%)		
Indication for PCI									0.58	0.81
Elective	26	(40.0%)	35	(43.8%)	37	(41.1%)	34	(42.5%)		
Unstable angina	11	(16.9%)	6	(7.5%)	14	(15.6%)	14	(17.5%)		
Non-STEMI	25	(38.5%)	32	(40.0%)	34	(37.8%)	29	(36.3%)		
STEMI	3	(4.6%)	7	(8.8%)	5	(5.6%)	3	(3.8%)		
GPIIb/IIIa type									0.88	0.21
None	38	(58.5%)	47	(58.8%)	53	(58.9%)	44	(55.0%)		
Abciximab	26	(40.0%)	30	(37.5%)	37	(41.1%)	32	(40.0%)		
Tirofiban	1	(1.5%)	2	(2.5%)	0	(0.0%)	4	(5.0%)		
Lesion length, mm	14.0	(6.4)	13.3	(7.0)	13.8	(8.2)	14.5	(6.4)	0.49	0.98
Stent length, mm	19.2	(6.9)	20.1	(9.2)	20.7	(10.2)	21.2	(8.4)	0.24	0.55

Cobalt chromium, CoCr; stainless steel, SS.
Count data shown as: count (%); comparisons: Fisher's exact test.
Numeric data shown as: mean (SD); comparisons: independent samples t-test.

Table 2
Vessel measurements (target lesion).

	Placebo				Prednisolone				Drug				Stent			
	CoCr		SS		CoCr		SS		Prednisolone–Placebo				SS-CoCr			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Diff.	95% CI		p	Diff.	95% CI		p
Reference diameters, mm																
Pre-PCI	3.19	(0.41)	3.13	(0.43)	3.21	(0.44)	3.21	(0.41)	0.06	−0.03	0.15	0.21	−0.03	−0.13	0.06	0.51
Post-PCI	3.24	(0.39)	3.13	(0.39)	3.29	(0.43)	3.27	(0.35)	0.10	0.01	0.19	0.03	−0.07	−0.16	0.02	0.13
6-month	3.05	(0.42)	3.02	(0.40)	3.08	(0.43)	3.09	(0.37)	0.05	−0.04	0.15	0.28	−0.02	−0.11	0.08	0.75
Minimum luminal diameters, mm																
Pre-PCI [A]	0.97	(0.46)	0.93	(0.41)	0.95	(0.46)	0.95	(0.41)	0.00	−0.10	0.10	0.99	−0.02	−0.11	0.08	0.74
Post-PCI [B]	3.02	(0.33)	2.98	(0.37)	3.04	(0.42)	3.04	(0.35)	0.05	−0.04	0.13	0.29	−0.03	−0.11	0.06	0.50
6-month [C]	2.04	(0.49)	1.91	(0.62)	1.96	(0.57)	2.05	(0.57)	0.03	−0.10	0.17	0.61	−0.01	−0.14	0.12	0.87
Acute Gain [B]-[A]	2.05	(0.50)	2.04	(0.47)	2.10	(0.54)	2.09	(0.47)	0.05	−0.06	0.16	0.42	−0.01	−0.12	0.10	0.85
Late loss [B]-[C]	0.95	(0.37)	1.08	(0.56)	1.13	(0.53)	0.99	(0.50)	0.04	−0.08	0.16	0.49	−0.02	−0.13	0.10	0.79
Net gain [A]-[C]	0.97	(0.59)	1.08	(0.58)	1.10	(0.62)	1.03	(.68)	0.04	−0.10	0.19	0.57	−0.01	−0.16	0.13	0.87
Diameter stenosis, %																
Pre-PCI	69.6%	(14.0%)	70.1%	(12.6%)	70.5%	(13.8%)	70.7%	(11.2%)	0.7%	−2.1%	3.6%	0.62	0.3%	−2.5%	3.2%	0.83
Post-PCI	6.9%	(6.4%)	5.1%	(5.2%)	7.2%	(6.6%)	7.1%	(5.6%)	1.3%	0.0%	2.6%	0.06	−1.0%	−2.3%	0.4%	0.15
6-month	33.4%	(12.3%)	36.6%	(18.7%)	36.5%	(16.2%)	33.9%	(15.3%)	0.1%	−3.6%	3.8%	0.97	0.0%	−3.7%	3.7%	0.98

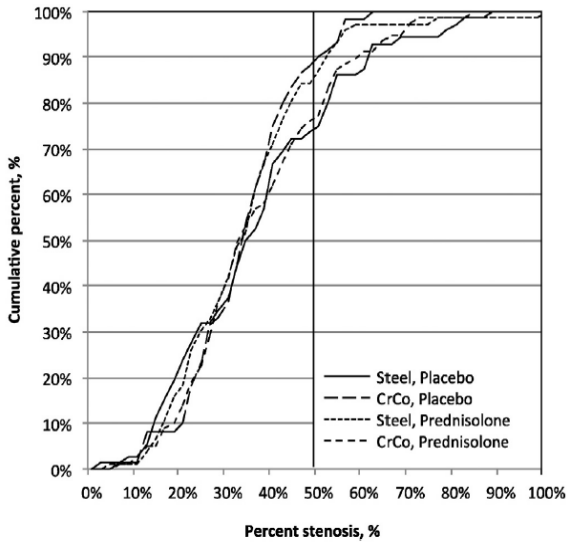


Fig. 2. Target lesion stenosis at six months.

8% (p = 0.23) for BMS alone (n = 125) compared to BMS plus oral prednisone (n = 125) [25].

In both IMPRESS and CEREA-DES, the incidence of a raised CRP prior to treatment was higher than in our study (28%), suggesting that this might be an important feature to identify a group of patients likely to get a clinically important effect. Even though we included a relatively high proportion of patients following an acute coronary syndrome our results suggest that upstream steroid therapy will have no impact on restenosis in a population where the pre-procedural hs-CRP is not known. Both IMPRESS and CEREA-DES utilised a high dose steroid regimen (reducing regimen of 1 mg/kg for the first 10 days, 0.5 mg/kg from day 11 to day 30 and 0.25 mg/kg from day 31 to 45). They did not include patients with diabetes. In our study, we included patients with diabetes and this influenced the steroid regimen, which was selected after discussion with our endocrine team to provide an effective anti-inflammatory dose used in other areas of medicine using a lower total and maximum dose of steroid in the early phase of treatment whilst minimising the risk of metabolic side effects. However, it is noteworthy that the results of the IMPRESS-LD study suggested that higher dose intensity for a longer period of time was required to reduce restenosis. The "low-dose" regimen in this small study itself included a loading of 1 mg/kg for the first five days of treatment [26]. This may partly explain the difference in our findings. Prednisone (which is metabolised to prednisolone) was well tolerated but in our study, with more patients, we saw an increase in hyperglycaemia in patients on prednisolone, even amongst those without known diabetes. The potentially greater anti-inflammatory activity with higher doses of prednisolone may therefore come at the cost of increased adverse effects. It is also possible that any benefits from an anti-inflammatory reaction might be countered by a positive effect on tissue proliferation.

We also compared the use of thinner strut cobalt alloy stents with stainless steel stents. In The Intracoronary Stenting and Angiographic Results Strut Thickness Effect on Restenosis Outcome (ISAR- STEREO) trial, thinner strut SS stents compared with thicker strut stents with a similar design had significantly less late lumen loss and BAR (15% vs. 26%, p = 0.003) [11]. Similarly the ISAR-STEREO 2 trial showed that thicker strut SS stents with a different design resulted in more restenosis compared to thin strut stents (31% vs. 18%, p < 0.001) [12]. We tried to minimise other stent design factors by using stents of similar design (Multilink) but composed of the two different alloys. In our study, there was no significant reduction in restenosis rates in the thinner strut CoCr stent. The difference in strut thickness was more marked in the ISAR-STEREO trials (50 μm vs. 140 μm) compared to our study (81 μm for the CoCr vs. 90-125 μm variable strut thickness system for the SS stent which is thicker in straight areas and less in areas where the stent needs to bend). It also may be that the expected reduction of restenosis due to reduced strut thickness with CoCr might have been countered by some other unknown factor. Although our study did not show an advantage for the lower strut thickness stent using the CoCr alloy, it did not show a disadvantage and there may be other advantages from using the cobalt alloy, especially in improving trackability.

Only one other single centre randomised study from Brazil has compared the influence of metal alloy (SS vs. CoCr) on restenosis. In keeping with our findings there was no difference in this outcome [27]. Their study design was different from our study in that both types of stents were implanted in the same patient but either in different vessels or in the same vessel if a gap greater than 10 mm could be left between the stents. There was also a larger proportion of patients with diabetes (36%) and higher rates of restenosis (34% vs. 32% SS compared to CoCr, p = 0.80) than in our study. Moreover, a range of different SS stents were used in the comparison group with a considerable range in strut thickness. There is scant experimental data on the subject. A small non-randomised animal study comparing SS (120 μm) and CoCr (90 μm) stents implanted into normal porcine coronary arteries did

Table 3
Study events.

	Placebo, N = 145				Prednisolone, N = 170				Drug			Stent		
	CoCr, n = 65		SS, n = 80		CoCr, n = 90		SS, n = 80		Placebo	Pred.		CoCr	SS	
	Count	%	Count	%	Count	%	Count	%	%	%	p	%	%	p
Primary endpoint[a]														
Restenosis (by any measure)+	7	(11.7%)	19	(26.4%)	18	(22.8%)	13	(17.1%)	19.7%	20.0%	1.00	18.0%	21.6%	0.46
In-segment average	7	(11.7%)	19	(26.4%)	18	(22.8%)	13	(17.1%)	19.7%	20.0%	1.00	18.0%	21.6%	0.46
Secondary endpoints														
Target lesion revascularisation	1	(1.5%)	9	(11.2%)	5	(5.6%)	6	(7.5%)	6.9%	6.5%	1.00	3.9%	9.4%	0.07
Target vessel revascularisation	2	(3.1%)	9	(11.2%)	6	(6.7%)	6	(7.5%)	7.6%	7.1%	1.00	5.2%	9.4%	0.19
Any endpoint or SAE	8	(12.3%)	20	(25.0%)	20	(22.2%)	13	(16.3%)	19.3%	19.4%	1.00	18.1%	20.6%	0.67
MACCE														
Composite	2	(3.1%)	10	(12.5%)	6	(6.7%)	6	(7.5%)	8.3%	7.1%	0.83	5.2%	10.0%	0.14
Death	0	(0.0%)	1	(1.3%)	1	(1.1%)	0	(0.0%)	0.7%	0.6%	1.00	0.6%	0.6%	1.00
MI	1	(1.5%)	1	(1.3%)	1	(1.1%)	0	(0.0%)	1.4%	0.6%	0.60	1.3%	0.6%	0.62
CVA	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0.0%	0.0%	-	0.0%	0.0%	-
Target vessel revascularisation	2	(3.1%)	9	(11.3%)	6	(6.7%)	6	(7.5%)	7.6%	7.1%	1.00	5.2%	9.4%	0.19

Count data shown as: count (%); comparisons: group %, Fisher's exact test.
MACCE, major adverse cardiovascular cerebrovascular events; MI, myocardial infarction; CVA, cerebrovascular accident.
[a] Analysed as target lesion (i.e. one lesion per patient) + 287 patients completed final follow-up angiography (CoCr/placebo, n = 60; SS/placebo = 72; CoCr/prednisolone = 79; SS/prednisolone = 76).

Table 4
Study markers.

	Placebo				Prednisolone				Drug			Stent		
	CoCr		SS		CoCr		SS		Prednisolone–placebo			SS–CoCr		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	95% CI		p	95% CI		p
hs-CRP, mg/L														
Admission	6.31	(14.53)	8.32	(13.11)	5.39	(11.77)	6.36	(15.07)	−4.90	1.72	0.35	−1.73	4.83	0.35
Pre-procedure	5.36	(12.77)	6.66	(10.50)	4.51	(11.32)	6.69	(15.19)	−3.56	2.53	0.74	−1.22	4.83	0.24
7 days	7.25	(9.38)	7.57	(16.14)	1.86	(6.99)	0.96	(3.01)	−8.35	−3.61	<0.001	−2.31	2.62	0.90
30 days	4.11	(9.85)	3.33	(6.38)	5.79	(6.56)	7.03	(9.43)	0.78	4.65	0.006	−1.79	2.12	0.87
6 months	1.48	(1.77)	3.29	(4.31)	2.45	(4.51)	4.36	(12.82)	−1.09	2.79	0.39	−0.15	3.69	0.07
HbA1c, %														
Admission	5.75	(0.85)	5.86	(0.97)	5.83	(0.87)	5.71	(0.50)	−0.23	0.16	0.75	−0.21	0.18	0.88
7 days	5.76	(0.84)	5.81	(0.89)	5.97	(0.99)	5.88	(0.53)	−0.05	0.34	0.16	−0.23	0.16	0.73
30 days	5.72	(0.67)	5.75	(0.60)	6.01	(1.24)	5.95	(0.55)	0.05	0.44	0.016	−0.23	0.16	0.73
6 months	5.75	(0.67)	5.95	(0.83)	5.96	(1.14)	5.82	(0.51)	−0.17	0.24	0.75	−0.19	0.23	0.85
Time to 30 d FU (d)	37.6	(104.5)	32.6	(6.9)	40.9	(79.0)	28.4	(41.6)	−15.1	15.2	1.00	−24.0	6.1	0.24
Time to 6 m FU (d)	210	(37)	204	(37)	203	(34)	201	(28)	−12.9	3.0	0.22	−11.3	4.6	0.41

not find an advantage of CoCr compared to SS with regards to late lumen loss and neointimal area from histopathological samples [28].

Our trial, although factorial in design, was not powered to detect a stent-drug interaction but nonetheless found one for the binary angiographic restenosis outcome. Within the stainless steel group, there is a numerical reduction in restenosis by prednisolone whereas the opposite occurs in the chromium cobalt group. The weight percentage of nickel and molybdenum is higher in 316L SS than CoCr [29] and the release of these metal ions may trigger local immune and inflammatory responses in susceptible individuals [30]. Whilst this may provide a plausible basis for a stent-drug interaction, it is more likely that this observation is a chance finding.

5. Study limitations

The change in the pattern of PCI delivery over the course of the study, with a shift towards more acute cases and ad hoc PCI had an adverse influence on recruitment. Many patients were not eligible for the second randomisation. This was compounded by the rapidly increasing use of DES use, largely the result of a National Institute of Health and Care Excellence (NICE) recommendation that DES should be used in arteries less than 3 mm in diameter or lesions greater than 15 mm in length [31]. Patient concerns about side effects of prednisolone and the need for repeat coronary angiography were also factors. This ultimately led to the recruitment target not being met. We approached approximately four patients for every patient who consented to the first randomisation. Of those who consented, only about 1 in 3 was suitable for randomisation after angiography. However, based on the results observed, it is unlikely that a statistically significant difference would have been achieved if the recruitment target had been met.

Another potential limitation is lack of operator blinding to stent type. However, this would not have been easy to achieve considering the different appearances of the stents used and the primary endpoint of the trial, BAR, was assessed without knowledge of stent type deployed. Hence we do not believe this is a major failing. There was no core laboratory analysis of the angiograms but analyses were performed by a single research fellow separate from the clinical team. Statistical analysis was performed independently from the clinical team.

6. Conclusion

Our study showed that treating patients upstream with a moderately high dose of prednisolone to cover most of the period of inflammation associated with restenosis in BMS did not reduce the incidence of binary angiographic restenosis. In addition, there was no significant reduction in restenosis rates with stents composed of cobalt chromium alloy compared to stainless steel.

Funding sources

The trial was supported by an unrestricted research grant from Abbott Vascular and Cordis with research personnel support from the UK National Institute for Health Research Local Clinical Research Network.

Disclosures

Dr de Belder has received a travel grant from Abbott Vascular. No other author has a conflict of interest to declare.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

Acknowledgements

The trial was supported and governance provided by South Tees Hospitals NHS Foundation Trust.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2016.04.105.

References

[1] A. Farb, G. Sangiorgi, A.J. Carter, V.M. Walley, W.D. Edwards, et al., Pathology of acute and chronic coronary stenting in humans, Circulation 99 (1999) 44–52.
[2] C. Stettler, S. Wandel, S. Allemann, A. Kastrati, M.C. Morice, A. Schomig, et al., Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis, Lancet 370 (2007) 937–948.
[3] K. Hasegawa, H. Tamai, E. Kyo, K. Kosuga, S. Ikeguchi, T. Hata, et al., Histopathological findings of new in-stent lesions developed beyond five years, Catheter. Cardiovasc. Interv. 68 (2006) 554–558.
[4] E. Camenzind, P.G. Steg, W. Wijns, Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern, Circulation 115 (2007) 1440–1455 (discussion 1455).
[5] G. Nakazawa, M. Vorpahl, A.V. Finn, J. Narula, R. Virmani, One step forward and two steps back with drug-eluting-stents: from preventing restenosis to causing late thrombosis and nouveau atherosclerosis, JACC Cardiovasc. Imaging 2 (2009) 625–628.
[6] T. Rhen, J.A. Cidlowski, Antiinflammatory action of glucocorticoids—new mechanisms for old drugs, N. Engl. J. Med. 353 (2005) 1711–1723.
[7] P.W. Radke, C. Weber, A. Kaiser, A. Schober, R. Hoffmann, Dexamethasone and restenosis after coronary stent implantation: new indication for an old drug? Curr. Pharm. Des. 10 (2004) 349–355.
[8] G.W. Stone, B.D. Rutherford, D.R. McConahay, W.L. Johnson, L.V. Giorgi, R.W. Ligon, et al., A randomized trial of corticosteroids for the prevention of restenosis in 102 patients undergoing repeat coronary angioplasty, Catheter. Cardiovasc. Diagn. 18 (1989) 227–231.

[9] C.W. Lee, J.K. Chae, H.Y. Lim, M.K. Hong, J.J. Kim, S.W. Park, et al., Prospective randomized trial of corticosteroids for the prevention of restenosis after intracoronary stent implantation, Am. Heart J. 138 (1999) 60–63.
[10] F. Versaci, A. Gaspardone, F. Tomai, F. Ribichini, P. Russo, I. Proietti, et al., Immunosuppressive therapy for the prevention of restenosis after coronary artery stent implantation (impress study), J. Am. Coll. Cardiol. 40 (2002) 1935–1942.
[11] A. Kastrati, J. Mehilli, J. Dirschinger, F. Dotzer, H. Schuhlen, F.J. Neumann, et al., Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (isar-stereo) trial, Circulation 103 (2001) 2816–2821.
[12] J. Pache, A. Kastrati, J. Mehilli, H. Schuhlen, F. Dotzer, J. Hausleiter, et al., Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (isar-stereo-2) trial, J. Am. Coll. Cardiol. 41 (2003) 1283–1288.
[13] D.J. Kereiakes, D.A. Cox, J.B. Hermiller, M.G. Midei, W.B. Bachinsky, E.D. Nukta, et al., Usefulness of a cobalt chromium coronary stent alloy, Am. J. Cardiol. 92 (2003) 463–466.
[14] M.H. Sketch Jr., M. Ball, B. Rutherford, J.J. Popma, C. Russell, D.J. Kereiakes, Evaluation of the medtronic (driver) cobalt-chromium alloy coronary stent system, Am. J. Cardiol. 95 (2005) 8–12.
[15] A.K. Rao, C. Pratt, A. Berke, A. Jaffe, I. Ockene, T.L. Schreiber, et al., Thrombolysis in myocardial infarction (TIMI) trial-phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase, J. Am. Coll. Cardiol. 11 (1988) 1–11.
[16] L.D. Fisher, D.O. Dixon, J. Herson, R.K. Frankowski, M.S. Hearron, K.E. Peace, Intention to Treat in Clinical Trials, Marcel Dekker, New York, 1990.
[17] C.H. Hennekens, J.E. Buring, Epidemiology in Medicine, Lippincott Williams and Wilkins, Boston, 1987.
[18] D.L. DeMets, Statistical issues in interpreting clinical trials, J. Intern. Med. 255 (2004) 529–537.
[19] G. Molenberghs, G. Verbeke, Linear Mixed Models for Longitudinal Data, Springer-Verlaf, New York, 2000.
[20] J.L. Fleiss, Statistical Methods for Rates and Proportions, second ed. John Wiley and Sons, New York, 1981.
[21] F.A. Graybill, An Introduction to Linear Statistical Models, McGraw-Hill, New York, 1961.
[22] V. Ferrero, F. Tomai, F. Versaci, M. Feola, I. Proietti, A. Rognoni, et al., Long-term results of immunosuppressive oral prednisone after coronary angioplasty in non-diabetic patients with elevated C-reactive protein levels, EuroIntervention 5 (2009) 250–254.
[23] P. Sardar, S. Chatterjee, D. Mukherjee, K.N. Garratt, Steroids for the prevention of restenosis in bare-metal stents—a systematic review and meta-analysis, J. Invasive Cardiol. 24 (2012) 98–103.
[24] C.J. Pepine, J.W. Hirshfeld, R.G. Macdonald, M.A. Henderson, T.A. Bass, S. Goldberg, et al., A controlled trial of corticosteroids to prevent restenosis after coronary angioplasty. M-Heart group, Circulation 81 (1990) 1753–1761.
[25] F. Ribichini, F. Tomai, G. De Luca, G. Boccuzzi, P. Presbitero, G. Pesarini, et al., Immunosuppressive therapy with oral prednisone to prevent restenosis after PCI. A multicenter randomized trial, Am. J. Med. 124 (2011) 434–443.
[26] V. Ferrero, F. Ribichini, A. Rognoni, P. Marino, S. Brunelleschi, C. Vassanelli, Comparison of efficacy and safety of lower-dose to higher-dose oral prednisone after percutaneous coronary interventions (the IMPRESS-LD study), Am. J. Cardiol. 99 (2007) 1082–1086.
[27] L.M. Abreu Filho, A.A. Forte, M.K. Sumita, D. Favarato, G.C. Meireles, L. Abreu Filho, et al., Influence of metal alloy and the profile of coronary stents in patients with multivessel coronary disease, Clinics (Sao Paulo) 66 (2011) 985–989.
[28] K. Milewski, A. Zurakowski, J. Pajak, E. Pajak-Zielinska, L. Liszka, P.P. Buszman, et al., Comparison of thin-strut cobalt-chromium stents and stainless steel stents in a porcine model of neointimal hyperplasia, Med. Sci. Monit. 16 (2010) BR40–BR44.
[29] G. Mani, M.D. Feldman, D. Patel, C.M. Agrawal, Coronary stents: a materials perspective, Biomaterials 28 (2007) 1689–1710.
[30] R. Koster, D. Vieluf, M. Kiehn, M. Sommerauer, J. Kahler, S. Baldus, et al., Nickel and molybdenum contact allergies in patients with coronary in-stent restenosis, Lancet 356 (2000) 1895–1897.
[31] Nice technology appraisals [TA 152] national institute for health and care excellence, https://www.nice.org.uk/guidance/ta152/chapter/1-Guidance2008 (accessed 30 October, 2015).

Ethics

Durham University
School of Medicine, Pharmacy and Health

Shaped by the past, creating the future

Dr David Ekers
Clinical Senior Lecturer
Chair, School of Medicine, Pharmacy and Health Ethics Sub-Committee

Zulfiquar Adam
School of Medicine, Pharmacy and Health
Durham University

10th February 2015

Dear Zulfiquar,

Re: Steroids Against Restenosis Study (STARS)

Thank for your application to the Durham University SMPH Ethics Sub-Committee relating to the above study. Based upon the information you have supplied to us that the original application has received full NHS REC approval and your analysis is fully included in that application, I am happy to confirm no additional application to the SPMH Ethics Sub-Committee will be needed.

Should any additional sub studies be proposed or analysis that falls outside the NHS REC approval, Chairs approval will need to be reviewed.

Good luck with your analysis and please contact me if you require any further information.

Kind regards,

David Ekers

Patient information sheet and consent form

South Tees Hospitals NHS
NHS Foundation Trust

Cardiology Research / Cardiothoracic
The James Cook University Hospital
Marton Road
Middlesbrough
TS4 3BW

www.southtees.nhs.uk
Tel: 01642 282410

PATIENT INFORMATION SHEET

The STARS Trial
[STeroids Against Re-Stenosis]

Introduction

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

What is the purpose of the study?

Your doctors have decided that you should be investigated with a special x-ray test called an angiogram to show if the heart arteries are narrowed. A fine, hollow tube called a catheter is inserted into an artery in your groin or forearm and is gently guided through the blood vessels. A dye is then injected into the blood vessels and X-rays taken from several angles. In addition Intravascular ultrasound (IVUS) may be performed before and after your angioplasty. This is a test that bounces high frequency sound waves off blood vessels in the heart. This provides a picture of the blood vessels, showing any narrowing's.

These tests provide the heart specialist with important information about treatment options, one of which is angioplasty, also known as percutaneous coronary intervention. This involves making the blood vessels wider by balloon treatment followed by insertion of a metal stent, to act as scaffolding. This procedure is very similar to the angiogram although it does take slightly longer. You may already have undergone angiography and have been admitted for an angioplasty procedure.

Although angioplasty and stenting is a successful treatment, about 20-25% of patients can develop angina within 6-months due to further narrowing of the artery at the site of the stent. This is known as instent re-stenosis and is thought to be due to inflammation in the wall of the blood vessel. Steroids are very good at reducing inflammation and are commonly used for this reason in many conditions. We hope

that by using a short course of steroid tablets and/or a newly designed stent at the time of your angioplasty, we can reduce the chances of future problems due to stent narrowing and reduce the chances of your symptoms recurring.

We plan to recruit 548 people into this study.

Why have I been chosen?

You have been chosen, as you are due to have a coronary angiogram and/or angioplasty. If your heart specialist decides after the angiogram that you do not need an angioplasty then you will not need to take any further **active** part in the study.

Do I have to take part?

Taking part in the study is voluntary. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part, you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive.

What will happen if I take part?

A heart doctor will see all patients before the angioplasty procedure. You will have a screening examination where you will be asked about your medical history, you will have a physical examination, electrocardiogram (heart tracing) and blood tests. This is all part of your routine care. The study will be discussed with you and if you agree to take part in the study further blood samples would be taken on day 1, day 3 (for patients living in the Teesside area only), day 7, day 30 and 6 months after the angioplasty. We will also invite you back for a clinic review on day 7, and day 30 after the angioplasty. Each additional blood test involves removing an extra 6mls of blood (about 1 teaspoon).

As part of your routine care you will need to take certain 'anti-platelet' drugs to help reduce the risk of blood clots forming around the stent after the angioplasty. (Platelets are tiny particles in the blood, which are the first step in forming blood clots that may block the new stent. Anti-platelet drugs block this effect). You will be given aspirin and another anti-platelet drug called clopidogrel. You will take clopidogrel for between 4 weeks and 1 year, depending on the type and number of stents that you have.

If you take part in the study, you will be given two extra drugs to take for a period of 4 weeks. A short time before your angioplasty a computer will determine which tablets you get. This process is called randomisation, which is like choosing the treatment by tossing a coin. One group of patients will receive a combination of steroid tablets plus a stomach-protecting tablet. The stomach-protecting tablet is given because the combination of steroid tablets together with aspirin and clopidogrel might lead to damage to the lining of the stomach. The other patients will receive a combination of placebo tablets (dummy tablets containing no drug) plus the stomach protecting tablets. A placebo is a dummy treatment, which looks like the real thing but does not contain the drug. It contains no active ingredients. It is included in the study, as some patients may feel better by simply taking a tablet. If we see a benefit

in the study we need to work out how much is due to this placebo effect and how much is due to the steroid tablets.

We will not know whether you have received the steroids or the dummy tablets until the end of the study. The tablets will start the day before the angioplasty. At the time of the angioplasty you will receive one of two stents, a standard stainless steel stent or a new cobalt stent. Both of these stents are currently used in clinical practice but it is not known whether one stent is better than another. The computer will also determine the choice of stent.

A repeat angiogram will be performed 6 months after the angioplasty to check for any evidence of stent narrowing. If you develop any symptoms before 6 months you will undergo a repeat angiogram as per normal clinical practice.

The risk of coronary angiogram

There are some small risks associated with an angiogram. Some patients have very severe disease in their heart blood vessels or in the vessels through which we have to pass to take the pictures. As a result of this or other factors, the internal circulation can be damaged. However the chances of any major problems such as a stroke, heart attack, or problems with the circulation of your leg or arm, are extremely small. Rarely, the rhythm of the heart can change but this is usually only short-lived and can easily be corrected. The radiation risk from the repeat coronary angiogram is extremely low. For example, the radiation dose from the coronary angiogram is similar to that received from the atmosphere over 10-months for the average UK resident.

Side effects of a coronary angiogram

Sometimes you can have a reaction to the dye that we use. Usually this takes the form of a mild nausea, or a minor skin rash or itching. In a few cases the skin rash can be more prominent but it usually settles very quickly in response to tablets that we give under these circumstances. Very rarely, severe allergic reactions can occur (less than 1 in 40,000). The risk of damaging part of the internal circulation of your body is less than 1 in 2,000.

The benefits of repeat coronary angiography

Once we have the results, we can discuss our findings with you and the options for treatment to improve your quality of life and reduce symptoms. You may not need any further treatment.

Side effects of steroid tablets

Steroid tablets are used very commonly in many patients and serious side effects are rare. In some patients steroid tablets can cause the blood sugar levels to rise whilst you are on the tablets (for this study that is 4 weeks). After you have had your angioplasty, and before you go home, we will teach you how to check your blood sugar levels at home. You will be given a contact telephone number for the cardiology research department and on call doctor plus an instruction sheet on when to check your glucose level and when to seek advice. For most patients steroid tablets

do not cause an increase in blood sugar levels. In some patients, steroids can lead to swings in mood (either up or down) and some patients can feel generally unwell. However the course of steroids is only for a short time.

What do I have to do?

If you agree to take part, you will need to carefully read this information sheet and sign a consent form. You will have to take the study drugs for 28 days (4 weeks). You will need to measure the glucose level of your blood 3 times a week. There will be 2 extra clinic visits over standard care, lasting 20-30 minutes each. We will ask you to attend for an angiogram to check your arteries at 6 months.

What is the procedure that is being tested?

We hope to establish whether a short course of steroid tablets reduces the risk of the vessel re-narrowing after an angioplasty. In addition, we are trying to determine whether re-narrowing is more or less likely with one form of stent over another. We hope that the use of steroid tablets at the time of your angioplasty reduces the risk of you developing stent narrowing and the recurrence of your symptoms. If they do then we may be able to change how we treat patients undergoing angioplasty and improve how well they do in the future.

What are the possible benefits of taking part?

There may be no benefit to you personally. We hope that the use of steroid tablets at the time of the angioplasty reduces the chance of stent narrowing developing, and the recurrence of symptoms of chest discomfort due to angina. We will only know at the end of the study which treatment you received.

Will my taking part in this study be kept confidential?

All information collected about you during the course of the research study will be kept strictly confidential. Your name and address will not be disclosed outside the hospital.

Your GP will be notified of participation in the study as well as any other doctor who is currently treating you.

As part of the study copies of your angiography films will be sent to an angiography core lab for review. If you have been asked to undergo an intravascular ultrasound evaluation, these images will also be sent to the core lab for review. These films and images may contain your full name.

What will happen to the results of the research study?

We expect to publish the results in a medical journal, but no reference will be made in any publication to any individual patient.

Important: What would happen should something go wrong?

If you have any complaints during the study as to your treatment by the members of staff e.g. doctors, nurses etc you can report this through the NHS complaints procedure. This would be an extremely unlikely event and should you wish to discuss this further with the doctor treating you this can be arranged. The hospital (The James Cook University Hospital) can advise on this.

In the unlikely event where you can prove negligence, patients will be covered by the South Tees Hospitals NHS Trust. In addition clinical staff involved in the conduct of the trial have personal professional insurance cover and will be happy to discuss any issues with you in person. Your right at law to claim compensation for injury where you can prove negligence is not affected by participation in this study.

There is no cover for harm (caused by an unexpected event associated with taking part in the study), which is no-one's fault. If a no-fault injury occurs the trial sponsors, South Tees Hospitals NHS Trust will not be held responsible. It will not be possible to claim damages against the trust.

Contact for Further Information

Please feel free to discuss the study with a member of the research team listed below,

Dr A Turley	Consultant Cardiologist
Dr M deBelder	Consultant Cardiologist
Dr S Jones	Consultant Endocrinologist
Professor R Bilous	Professor of Clinical Medicine and Endocrinology

All members of the research team can be contacted via Telephone
Dr A Turley: 01642 850 850 ext. 52410
Dr M deBelder: 01642 850 850 ext. 54620
Cardiology Research Department 01642 850 850 ext. 52410

Thank you for taking the trouble to read this. If you agree to take part you will be given a copy of this information sheet and the consent form to keep.

Date: May 2010. Version 9.0

REC reference number: 04 MREC02/61

South Tees Hospitals NHS
NHS Foundation Trust

Cardiology Research / Cardiothoracic
The James Cook University Hospital
Marton Road
Middlesbrough
TS4 3BW
www.southtees.nhs.uk
Tel: 01642 282410

Centre Number:
Study Number:
Patient Identification Number for this trial:

PATIENT CONSENT FORM

Title of Project: **The STARS Trial**
[Steroids Against Re-Stenosis]

Name of Researcher	
Dr A Turley	Consultant Cardiologist
Sister B Atkinson/L Thompson	Cardiology Research Sister/Nurse
Dr M de Belder/Dr A Sutton	Consultant Interventional Cardiologists
Dr R Wright/Dr J Hall/Dr D Muir	Consultant Interventional Cardiologists

Your GP will be informed of enrollment into the study

Please initial box

1. I confirm that I have read and understand the information sheet dated May 2010 Version 9.0 for the above study and have **had the opportunity to ask questions.** ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that sections of any of my medical notes may be looked at by responsible individuals or from regulatory authorities where it is relevant to my taking part in research. ☐
   I give permission for these individuals to have access to my records. ☐
4. I understand that there is no insurance cover for non-negligent harm for the above study. ☐
5. I agree to take part in the above study-**The STARS Trial**. ☐

6. I agree to take part in **STARS Trial-IVUS sub-study**. ☐

----------	----------	----------
Name of Patient	Date	Signature
----------	----------	----------
Name of Person taking consent (if different from researcher)	Date	Signature
----------	----------	----------
Researcher	Date	Signature